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PANEL DISCUSSION ON DIABETES MELLITUS IN THE AGED*

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Panelists: ‡ IRVING GRAEF, M.D., THOMAS H. MCGAVACK, M.D., HERBERT POLLACK, M.D., HOWARD ROOT, M.D., BEVERLY C. SMITH, M.D. AND EDWARD TOLSTOI, M.D.

MODERATOR KINSELL: The problem of diabetes is with us constantly, whether we are interested in pediatrics, geriatrics, or just people. Diabetes lends itself to a group approach. The disease affects so many organs and systems that the opinions and experience of many men are necessary in order to see the problem in its entirety and to approach it constructively.

The panelists have extensive backgrounds, interest, and experience in this disease. They will speak on certain aspects of it and then will discuss points of agreement and disagreement in terms of a general plan of organization. The third phase of the discussion will be devoted to the consideration of specific questions from the audience.

Dr. Root, will you begin today's discussion of diabetes in the aged with a presentation of the over-all problem?

DR. ROOT: Diabetes in persons 60, 70 and 80 years of age has become an increasingly important problem in hospital populations and in office practice as well.

The problem is numerically greater than ever before. Also, it is practically important in terms of treatment, diet regulation, and the management of complications. In surgical complications such as fractures, there are the problems of

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pressure necrosis and failure to heal. In the aged, complications affect the eyesight, general health and cardiac status.

First, let me say a word about the incidence of diabetes and its detection at all ages. Approximately 1 per cent of the population has it, and another 1 per cent has it but does not know it. In the wards of hospitals in Boston which we recently surveyed, in a twelve-month period there were 500 patients with surgical lesions of the foot who proved to have diabetes. Ten per cent of them admitted no previous knowledge of the disease. The cost of that group of cases is tremendous, not merely in terms of dollar costs paid by the patient, but in terms of medical and surgical time.

The diagnosis of diabetes is still a problem. A good test for sugar in the urine does not exist. With present procedures, a frank case of diabetes can be detected, but not a borderline case. We still are hampered by inadequacies of the fasting blood sugar method.

In 1954, five hospitals in Boston tried the experiment of determining the blood sugar level of middle-aged of patients without diabetes, one hour after breakfast. Five per cent of the first 300 patients had diabetes which was unrecognized and untreated simply because they had been tested previously by the fasting blood sugar method—which is sure to miss in some cases of diabetes.

In the last two or three years, a striking increase has occurred in hospital admissions of aged people. In five years, the number of patients over 70 years of age has increased by 50 per cent. A large proportion of hospital patients have diabetes in association with foot, eye, or kidney lesions, all really stemming from the condition existing a few years earlier when diabetes was present but not recognized or treated.

Moderator Kinsell: In order to approach the problem of diabetes, it is first essential to make a diagnosis, and to have the necessary machinery for making it. Dr. Pollack will discuss briefly the features of the diagnosis and differential diagnosis of diabetes, with particular reference to the disease as it occurs in middle-aged and elderly people.

Dr. Pollack: Before criteria for diagnosis can be established, what we are trying to diagnose must be defined. The question as to whether diabetes is a specific disease, whether it is a disease syndrome, or whether it represents a multiplicity of diseases can be put aside temporarily. For practical, clinical purposes, what we should like to know is whether or not there has been sufficient interference with carbohydrate metabolism in the patient to affect his physiology to the degree that his existence is threatened, or there is inability to lead a normal, healthy, happy life.

The usual definition is that diabetes is a disease syndrome associated with irreversible hyperglycemia and the manifestations that accompany it.

Diabetes in the aged—or the condition that we call diabetes in the aged—is usually quite different from the classic diabetes seen in younger persons. In the younger age group, the onset of diabetes can be sudden and dramatic, with polyuria, polyphagia and weight loss. In elderly persons, this type of onset is seldom seen.

Glycosuria, because of its insidious nature, can be present for many years

without the affected person being aware of it. However, the lack of dramatic clinical symptoms and signs does not mean that the disease is having no harmful effect. The most difficult problems are the infections and ulcers of the leg that occur in people in whom glycosuria is easy to control. There is no relation between the severity of the condition, its influence on the health and life of the individual, and the degree of glycosuria.

The usual clinical diagnostic criteria depend upon the presence of sugar in the urine and upon a high concentration of sugar in the blood. In the past, investigators have been somewhat confused by the various methods for determining blood sugar concentration. The differentiation between the so-called true method and the standard Folin method, and the complicating factor of whether the blood is venous or capillary, make diagnosis difficult.

In order to determine from the laboratory report whether or not diabetes is present, the history of the particular blood or urine sample should be known. As Dr. Root pointed out, diabetes in older persons can be missed easily because of the so-called benign nature of glycosuria, and because of the fact that in overnight fasting, as patients say, the blood has had a chance to clear and the urine does not show sugar. The urine specimen must be collected at least one and a half hours after a meal containing a full carbohydrate intake, and the investigator must know whether the blood specimen is venous or capillary. The significance of a blood sugar level of 200 mg. per 100 ml. postprandially in a venous sample is entirely different from that of a similar blood sugar value in a capillary sample.

All these factors must be taken into consideration in establishing the diagnosis of diabetes.

Clinically, a patient with any type of chronic leg ulcer or callus that has ulcerated should immediately be suspected of having diabetes and be subjected to thorough examination of the blood and urine, including a glucose tolerance test if the blood sugar values are indeterminate.

The importance of making the diagnosis in this group of patients is, as Dr. Root pointed out, self-evident. Prognosis and therapy are entirely different for a patient with a foot infection who has diabetes than for one who does not have diabetes. Problems arise because of long periods of hospitalization, bed sores, and other types of trophic alterations. Diabetes is a serious complication, and requires aggressive handling. It is important to determine as early as possible whether or not diabetes is present as a complication of the condition that brought the patient to the hospital.

Several forms of hyperglycemia and glycosuria that occur in this age group do not represent true diabetes mellitus. A few years ago, we reported a large series of patients who had hyperglycemia and glycosuria for periods up to six weeks following acute coronary occlusion and shock. These patients did not have diabetes nor the complications associated with diabetes. The hyperglycemia and glycosuria disappeared. When the history of such individuals is unknown, they must be suspected of having diabetes and treated as though it were present, even though the syndrome will disappear in the course of time as the shock episode subsides.

MODERATOR KINSELL: Dr. Tolstoi, will you please indicate some of the funda-

mentals involved in a therapeutic approach to diabetes in middle-aged and elderly patients.

DR. TOLSTOI: I shall limit myself to the treatment of patients with diabetes. They belong in two categories: those who live with their family, and those who live by themselves. The difficulties for those who live alone are obvious.

I would not treat vigorously patients without symptoms of diabetes; that is, those who have only glycosuria, who maintain their weight, and who are not bothered by frequency except because of prostatism. Such a man or woman can eat a normal diet, similar to the one he is accustomed to eating. It must be nutritious, include ample vitamins, and contain some milk. Decalcification takes place more rapidly in elderly persons than in younger ones.

If the patient lives with his family, he should be told to eat whatever the others do. For breakfast, he may have the juice of an orange or a serving of fruit, an egg or two, a piece of toast, and tea, coffee or milk. For lunch, he may have a sandwich or a salad, tea or coffee, and a bit of fresh fruit for dessert. At dinner, he may partake of whatever the family has to eat. He probably will fare well, even though he has glycosuria—provided he feels well and is symptom-free.

If any of the symptoms of diabetes or even weakness develops (many diabetics say that they are tired at the end of the day), the patient should have small doses of insulin. In addition to his usual diet, he should take about 10 units of a slow-acting insulin, such as NPH, Lente, or globin. Which preparation to prescribe matters not, as long as one is familiar with it. If the symptoms do *not* clear with the use of 10 units daily, the dosage should be increased by 5 units every three or four days until they do clear.

We agree that glycosuria in older people is a protective mechanism. I would rather tolerate some glycosuria than risk an insulin reaction or a hazard from a cardiologic point of view.

The patient who must live alone has a difficult problem. Diet must be discussed more carefully with him. He has to administer his own insulin, which involves mechanical difficulties. Kits for insulin administration that he can carry with him are available. A recent development is a receptacle for alcohol used in sterilization, so that the patient can dispense with boiling the syringe daily. If he has poor eyesight, a member of his family can fill three or four syringes for him every three or four days, and these can be stored in the refrigerator. Thus he can avoid the problem of drawing insulin to the proper level. Magnifying devices attached to the syringe improve visual acuity. Patients who live by themselves are told to get in contact with a physician the moment they have a gastro-intestinal upset, a cold, or a respiratory infection. The best place for them is in a hospital.

That is the general approach to diabetes in the elderly person living either with his family or alone, and trying to earn his livelihood in a large or small city.

MODERATOR KINSELL: One of the most interesting and encouraging developments of the last several years has been the increasing awareness that diabetes is not an isolated endocrine disease, but is part and parcel of the over-all picture of endocrine and metabolic disease. There is, perhaps, no metabolic disease about which we know as much as about diabetes mellitus.

Dr. McGavack will make some remarks about other endocrine functions that are associated with the disease, referring to controlled diabetes.

DR. MCGAVACK: For a long time, pathologists have been puzzled about the fact, that on occasion, there is a scarcity of evidence for the causative factors in deaths from diabetes. Secretions from endocrine glands other than the pancreas may be involved in one of two ways—they may either cause the diabetes or they may aggravate it.

Considering first the pituitary, the relationship of growth hormone to experimental diabetes is well known. Evidence seems to be increasing that growth hormone may play a significant part in diabetes in human beings. The influence of growth hormone is of vital interest in relation to the problems of the pregnant patient with diabetes and in relation to the child born of such a pregnancy. Growth hormone has a direct influence upon the pancreas. Many believe that it also affects the role of the adrenal cortex in relation to diabetes. The adrenal cortex is also involved through its responsiveness to pituitary ACTH. The resulting increase in corticoids may not only cause hyperglycemia and glycosuria experimentally, but also clearly aggravate an existing diabetes. In well-controlled diabetic patients, the control has been disturbed by the administration of corticoids.

On the other hand, correlation of the diabetic state with the levels of blood and urinary glucocorticoids is not so simple. In most well-controlled patients with diabetes, such values are normal. Even in poorly-controlled patients who are not in a state of acidosis, the total urinary excretion of adrenal steroids is not significantly disturbed. In many cases of acidosis or coma, the excretion of adrenal steroids is definitely increased for a short time.

It is interesting to observe the action of adrenocortical steroids in normal subjects as compared with diabetic subjects. For instance, we have studied the influence of the infusion of 20 per cent glucose into normal subjects before and after the oral administration of 200 mg. of cortisone daily for six days. Surprisingly, after cortisone treatment, the infusion produced glycosuria in association with a lower level of blood sugar. Moreover, the blood sugar level in the normal subjects did not rise as high after the use of cortisone as it did before. This is not true in the diabetic patient, in whom both the hyperglycemia and glycosuria are aggravated.

The role of the thyroid in the metabolic disturbances of diabetes is that of an accelerator. One well known action of thyroid hormone is to increase the conversion of glycogen to glucose and to mobilize protein moieties from muscle tissue preparatory to neoglucogenesis. The increased incidence of diabetes in hyperthyroidism attests to this action.

The role of the gonads in diabetes is far from clear. However, it is known that they can influence sugar tolerance and the diabetic state. In clinical practice, administration of estrogen has improved the carbohydrate tolerance of patients with diabetes. Cyclic variations in the production of estrogen in menstruating diabetic patients may result in alternating episodes of insulin shock and acidosis, despite a constant dietary and insulin regimen. These wide fluctuations can be stabilized by the addition of adequate doses of estrogen in most cases. The mech-

anism of this action is not clear, but it is probably an indirect one, in which the pituitary may play an important intermediary role.

The administration of testosterone has both improved and aggravated diabetes mellitus. Obviously, therefore, its action is indirect.

In conclusion, it seems important to emphasize the fact that a disturbance in a single function of one endocrine gland, such as the loss of insulin production in pancreatic diabetes, will have repercussions throughout the entire endocrine system.

MODERATOR KINSELL: We shall amplify some of the general aspects of endocrine dysfunction in diabetes in the course of the discussion.

Next, we shall consider vascular disease, with particular reference to the surgical aspects, in the middle-aged and elderly diabetic patient. This is a problem of vast importance from both a clinical and a theoretical standpoint. Dr. Smith, will you treat that phase of the problem?

DR. SMITH: I shall re-emphasize many things that you know, because this is an unfortunate group of elderly people who represent great expense to themselves and to their families. The high cost of their hospitalization has a definite influence upon therapy, and emphasizes the necessity for prophylaxis of conditions that precipitate surgical emergencies.

Some years ago, I examined the Presbyterian Hospital records in a group of surgical cases of diabetes and vascular disease, and found that each patient cost the hospital about $150.00.

Hospitals, particularly resident services, do not want these patients. I think the best way to solve this problem is to make the surgical diabetic service in the hospital so attractive to the members of the house staff that they will want some of these patients to treat. They should see them. They are going to encounter them, and they should be prepared to handle the specific problems involved.

The value of prophylactic treatment of the extremities of diabetic patients should be emphasized again and again. Local cleanliness and properly fitted shoes are imperative as aids in the prevention of acute pathologic changes which may arise from calluses, corns, and interdigital or nailbed infections. These conditions may occur spontaneously or may be the result of pressure from ill-fitting shoes. Prophylactic measures should be explained sufficiently often to ensure that they are included in the daily routine. The patient should be supervised frequently to see that the regimen is carried out. The femoral, popliteal, posterior tibial, and dorsalis pedis arteries should be palpated and the findings recorded in the patient's chart. If the distal arteries are not palpable, changes in the color of the leg upon elevation and depression, together with the time required for venous filling and emptying on the dorsum of the foot, will furnish valuable information as to the extent of the collateral circulation.

What can be done for patients with lesions of the extremities? Few peripheral vascular lesions occur in the upper extremities; they are most common in the lower extremities. That means the patients must be taken off their feet. They should be admitted to a hospital or cared for at home. Many times, no one is at home who can care for them effectively.

By the time the disease has reached the state in which the peripheral vessels are severely compromised, the patient's arterial system is affected in other places. If other specialists are not available, the surgeon himself must interpret the findings and treat the patient with regard to cardiac, ophthalmic, and kidney dysfunction.

Cultures should be made from any local exudative inflammation and the causative organism tested for sensitivity to antibiotics. Until this test is completed, a broad-spectrum antibiotic ointment may be used. In many instances, elevation of the leg and saline compresses (changed three or four times in twenty-four hours) will be effective.

In the case of a local lesion, what is the approach to the surgical problem? Harm may be done by overactive local treatment. Ointments and lotions may cause local maceration, if there is not sufficient local blood supply to enhance their effect.

As long as a local lesion manifests evidence of granulation, *i.e.*, of healing, and sequestration of the infected tissue is occurring, conservative treatment is justified. When a lesion requires surgical removal, the basic philosophy should be to preserve as much of the extremity as possible. Consider the problem of amputation of a toe; by the time osteomyelitis, suppurative arthritis, or tenosynovitis has developed, it will probably be necessary to amputate the toe and remove the cartilage of the metatarsal. Elderly people may spend six to eight weeks in a hospital before the site of a toe amputation heals. It is safer to have the site epithelialized before the patient is discharged. This is a serious economic problem. Once it is decided that the single or multiple local lesions, moist or dry, require surgical treatment, then we enter the realm into which Dr. McKittrick of Boston has led us in the last few years, and in which he has reported success.

The indication for the transmetatarsal operation must be clear, because in many instances complications occur. However, the transmetatarsal operation in general remains successful. Follow-up examination shows that most of these patients have a useful extremity. This procedure should always be considered.

For treatment of a fulminating infection in a patient with uncontrolled diabetes, a true guillotine procedure with no attempt at plastic closure is often the only life-saving measure available. It should always be borne in mind before a definitive amputation is performed in a patient with such an infection.

In the surgical approach and diagnosis, it is important to study possible preservation of a part and what that preservation will mean to the patient economically. First, amputation of the toe is considered; next, the transmetatarsal procedure; then, a true guillotine operation at the lower third of the leg; and lastly, amputation of the lower leg, preferably by a modified guillotine technic, leaving at least 4 inches of tibia.

I believe one should try to save these patients' knee joints. It has been my experience that the rehabilitation of below-the-knee amputees is more rapid and complete than that of thigh amputees. I seldom amputate above the knee. The time will come shortly when textbooks will not include the statement that the method of choice is supracondylar or thigh amputation. According to my

experience, it is difficult for thigh amputees to wear a prosthesis successfully. These patients are usually the victims of complications of diabetes, namely, arteriosclerosis of the cerebral, retinal, cardiac and renal arteries. They are usually weak, depleted and unstable. Most of them lack the courage necessary to master the use of a prosthesis. If the patient cannot use one easily, he becomes a bed or chair patient at home, and consumes the time of a family member, thus decreasing the earning capacity of the family.

I wish to make a plea for either a transmetatarsal operation or amputation below the knee when the procedure will not do such damage to the collateral circulation (the only arterial circulation that keeps the part alive) as to cause local necrosis.

I recently reviewed 50 cases of diabetic gangrene. The patients were operated on by me at the Presbyterian Hospital in New York City between the years 1930 and 1950, using a modified guillotine technic which I described in the *Archives of Surgery* in August 1933. The number of male and female patients were equal. The age distribution was as follows:

Age range (yrs.)	Per cent of patients
40 to 50	12
51 to 70	70
71 to 80	16
81 to 90	2

Six patients died in the hospital. Among the 44 survivors, 32 (72 per cent) successfully wore prostheses and resumed their preoperative status. Nine per cent did not wear them for financial reasons, but their stumps would have supported a prosthesis. Thus, a total of 81 per cent of the patients could have worn prostheses. Among the 12 bilateral amputees, 5 (48 per cent) wore prostheses on both legs. Three (6 per cent) of this group required reamputation. The length of survival was as follows:

Survival time (yrs.)	No. of patients	Per cent of patients
Less than 1	5	12
1 to 5	17	40
5 to 10	9	22
10 to 15	6	14
Over 15; still living	5	12
Died in the hospital	6	—
Lost to follow-up during first year	2	—

The results of observations over a long follow-up period (more than twenty years) appear sufficiently encouraging to warrant the removal from textbooks and the abolition from teaching institutions of the doctrine that amputation at thigh level is the treatment of choice for these patients.

Moderator Kinsell: One of the most startling, impressive, and exciting medical developments of the last twenty years is the conquest of infectious disease. This success highlights medical problems that remain to be solved. One of the most important is degenerative vascular disease, including the type that Dr. Smith has talked about, and many other manifestations as well.

Fundamental answers as regards any form of such disease are still to come. That makes life interesting, but it also makes it difficult for the patient with the disease and for the physician who must manage him.

In the diabetic patient, degenerative vascular disease is much the same as that which practically everyone gets if he lives long enough, but the incidence is much higher. This suggests, perhaps, that the diabetic patient should be studied particularly by students of arteriosclerosis and related conditions.

Another type of vascular disease is the so-called Kimmelstiel-Wilson syndrome, a condition that affects the kidneys in particular and has similar manifestations in the eyes.

Dr. Graef will discuss the medical forms of vascular complications that occur in the diabetic subject.

DR. GRAEF: The variability of diabetes as observed in the general medical population is impressive. At one extreme is the patient, about whom one cannot afford to be casual, who may have had diabetes over a long period of time as an incidental manifestation of a metabolic state, but who has no complications. Unfortunately, it is seldom possible to predict that a patient will remain at that benign extreme.

Another type is the asymptomatic diabetic patient. In the elderly person, the classic symptoms—polyuria, polydipsia, weight loss and fatigue—are not always present. The complications of diabetes, notably the vascular ones, bring these patients to our notice. A cerebral hemorrhage, an ischemic lesion of the foot, a change in vision due to retinopathy, or slow, persistent, progressive edema due to nephropathy may be the first indication. In a person with evidence of coronary disease, diabetes may have been latent or asymptomatic for years.

The patient with renal complications may suddenly experience renal failure and present evidence of uremia. Many of us regarded the first descriptions of the Kimmelstiel-Wilson syndrome with skepticism. Many of my colleagues in pathology were particularly skeptical; indeed, some of them insisted that the lesions were not specific. Today, however, most pathologists recognize that among diabetic patients, those who have the characteristic intercapillary lesions represent a group with a specific kind of complicated diabetes. We are all indebted to the students of this disease at Montefiore Hospital, because they have indicated that the manifestations of this syndrome are many and varied. Some patients with renal lesions have no renal disturbance, but have other signs of widespread capillary disease.

Large vessels with classic atheromatous plaques are found in persons both with and without diabetes.

We cannot be sanguine about the benign state of diabetes because it is hard to characterize.

I should like to call attention to the problem of diagnosis of vascular disease as it confronts the internist. It is necessary to recognize involvement of the aorta, of the femoral artery at its origin, or of the profunda branch, as the possible source of a lesion that begins asymptomatically in the toe. One should be aware that lesions in the abdominal aorta may give rise to symptoms of neurop-

athy from the toe to the buttock. Pain of sciatic distribution may be a manifestation of an aortic thrombotic process that is progressing slowly and affecting branches to the main nerve trunk.

Awareness of these possibilities has increased with knowledge. No disorder that I know of requires a fuller appreciation of the widespread distribution of these vascular complications.

To make earlier diagnosis possible, we must review our practices. I should like to touch upon something to which Dr. Root referred. Tradition has caused many institutions and practitioners to rely upon fasting blood sugar levels as an index of the diabetic state. Dr. Root pointed out the folly of this assumption. Let us look at hospital practice with respect to collecting urine samples. How many institutions obtain postprandial samples? The majority, to my knowledge, still collect urine samples in the morning. These are obtained virtually in the fasting state, for the hospital food of the night before was consumed by 6:00 P.M. Thus, there is no challenge to the carbohydrate metabolic mechanism that can be reflected in the glucose content of the overnight urine sample.

Some simple changes in these practices would help us all to detect diabetes earlier. A broader awareness of the distribution and frequency of asymptomatic vascular complications would enable us to treat diabetic patients before they become cripples and economically dependent.

MODERATOR KINSELL: While questions are being written by members of the audience and collected, the panel will engage in discussion. I suggest as a topic—and perhaps there is no more important topic and none less clear in this field—the possible prevention or postponement of vascular complications of the type just mentioned.

Do any of you believe that procedures can be carried out that will postpone, prevent, or lessen the incidence or severity of vascular complications?

DR. ROOT: That is a broad question.

I should like to re-define diabetes. Diabetes mellitus is not a hodgepodge; it is not a wastebasket; it is not a syndrome. Diabetes mellitus is a clinical disorder, the basic characteristic of which is hereditary. There is no diabetes without an hereditary factor. That statement has been made by other people—by Bertram in Germany, for instance.

Suppose in a patient with cancer from whom Dr. Smith has removed the pancreas, hyperglycemia and glycosuria develop and are treated by insulin. Dr. Smith has produced hypoinsulinism, but he has not produced diabetes mellitus. He does not, by removing the pancreas, provide the protoplasm of the patient with the capacity for transmitting diabetes to the next generation. That principle is basic in any discussion of prevention.

If persons with diabetes marry others with the disease, there will be more diabetes. At present, diabetes occurs in 20 per cent of the children of diabetic mothers before the age of 15 or 18 years. What is transmitted? Let me refer you to a recent book by Bell (Charles C Thomas, Publisher) entitled "Experimental Diabetes and its Relation to the Clinical Disease." It contains an excellent chapter on the present concept of what is hereditary in diabetes and on the various types of genes that may be involved.

I estimate that 1 out of every 3 men here either has diabetes or has a diabetic relative. In every audience I have come across, this has been true of about a third of the members.

What is inherited? Not merely the capacity for diabetes, but the capacity for neurologic and vascular lesions. Once the clinical state develops, an acceleration of the complicating factors takes place.

In a study of patients with uncontrolled clinical diabetes (hyperglycemia and acidosis) who took insufficient insulin and paid no visits to the doctor just because they felt well, we found retinitis and approaching blindness.

In the Massachusetts Division of the Blind, 18 per cent of the patients admitted in the year 1955 up to April 15, had diabetes. Five years ago, 8 per cent had diabetes. In New York State there is probably a similar increase in blindness among diabetic patients.

The increased incidence of blindness did not occur among elderly patients with glaucoma, or elderly diabetic patients with cataracts. The increase occurred in younger patients in their 30's and 40's. Such an increase is not necessary, and our data have convinced me that these lesions can be postponed.

DR. TOLSTOI: I think that some of those statistics reflect the fact that today young diabetic patients live longer than they used to, and we therefore see much more blindness in young diabetics. In the era before insulin, the diabetic patient died before the so-called complications or sequelae of diabetes had a chance to develop.

I do not know how to prevent or postpone these complications. There are data on record of patients who had the most meticulous chemical control, and yet these lesions developed. Conversely, there are data showing that in some patients with glycosuria and hyperglycemia these complications did not develop, even after twenty to twenty-five years.

In any large group of diabetics, a certain number will escape such lesions no matter how they are treated. Whether Dr. Root treats them well, or I treat them badly, they will escape. Maybe this indicates a different type of diabetes, and perhaps our knowledge is so inadequate at this particular point that our thinking has to be revamped, so that we shall be talking about the same thing. I am fairly certain that we are not talking about the same thing now.

A chance circumstance that impressed me concerns a young man who had hemorrhages in his eyes. It is an isolated case, but it may be a lead. (These hemorrhages, by the way, come and go irrespective of therapy. They may appear when the urine has been sugar-free for months, and disappear when the urine is loaded with sugar.) This particular young man at every visit had new microaneurysms and larger hemorrhages, but suddenly they disappeared, leaving healed yellow refractive spots. After several years of observation I still cannot see any hemorrhages in his retina. What is taking place in this patient? I do not know, for his living has not changed in any way.

I do not believe that Dr. Root's thinking differs from mine, and I am sure that mine does not differ from Dr. Root's or anyone else's. However, we have no common denominator as a basis for our thinking, and because of that there are apparent, but not real, differences of opinion.

I was much interested in Dr. Root's comments on heredity. I am sure he has a good point. However, we are left out on a limb, when a careful search of the family history of a diabetic patient reveals no evidence of diabetes. These cases puzzle me.

I agree with Dr. Root that heredity is important. I have had diabetic mothers and fathers with 4 or 5 diabetic children. How to manage this problem is rather difficult. Should such people be told not to marry? I believe our solution has to come from some other source.

MODERATOR KINSELL: I suspect that many of the differences in opinion on the management of diabetes are more apparent than real. I should like to raise a few specific questions and ask the panel for a general expression of opinion on them.

The disagreement concerning the management of the middle-aged and the older diabetic patient is less than in the juvenile diabetic.

Does the panel agree that, in a middle-aged or elderly diabetic patient who is overweight, weight reduction should be the primary objective in the over-all control of the diabetes? That, it seems, is at least one point of complete agreement. It may be the only one that we shall find.

DR. GRAEF: It is important to assess the patient's nutritional status before starting a weight reduction program. The educational needs and the psychologic status of the patient must be considered.

From a physiologic standpoint, it is important to be sure that the composition of the diet provides adequate protein. It is simple to reduce calorie intake in a gross fashion, but in a person with a metabolic disorder characterized by incomplete utilization of carbohydrate and fat, it is important not to oversimplify this regimen. Individuals who undertake a starvation routine are sensitive to infections, and may get into serious difficulty as a consequence.

Some people may be in conflict emotionally over the whole program. I am thinking about certain extremely obese persons who sense the alarm in the doctor's voice and are upset by the need to face the facts, especially if there has been contact with a diabetic relative. There should be an appreciation of the patient's needs, and a recognition of what he can do and how much he can provide.

Adequate protein is important, especially to the liver.

MODERATOR KINSELL: Will you indicate what you believe is adequate protein for a patient 60 years of age who has no obvious renal insufficiency and whose diet contains 800 to 1000 calories?

DR. GRAEF: Each patient must be assessed individually. Dr. Pollack has repeatedly emphasized the fact that protein deficits are hard to make up. They may be present even in persons who appear to be of normal or excess weight. If the diabetic patient is obese, ambulant, asymptomatic, and not doing heavy work, between 40 and 60 Gm. of protein would be a desirable amount in a diet containing 800 to 1000 calories.

DR. MCGAVACK: Perhaps some of the experiences of Dr. Kountz in studying the protein balance of such patients are applicable. He has found it practically

impossible to maintain protein balances in older persons with diets containing less than 1.25 Gm. of protein per Kg. of body weight.

Does Dr. Graef mean that we have to include 1.25 Gm. of protein per kilo of body weight in the diets of these older diabetic patients who are overweight, calculated on the basis of their ideal rather than their actual poundage?

DR. GRAEF: That is the basis for it. Weight reduction can occur under such a program, assuming that water and salt balances are normal.

MODERATOR KINSELL: We have been able to maintain positive nitrogen balance with 50 Gm. of protein and a total caloric intake of 600.

Before we take up the questions from the audience, perhaps some of the members of the panel would like to raise questions.

DR. POLLACK: I should like to ask Dr. Smith to expand his discussion of the surgical conditions of the foot, taking into account the condition of the other foot. In an elderly diabetic patient with an obvious lesion that may require surgery or amputation, the foot on the opposite side may present the beginnings of a similar lesion.

Would Dr. Smith care to discuss this situation?

DR. SMITH: That is a serious problem and one of the most difficult. It brings up the question of conservatism in regard to the bad foot. The active treatment of arterial deficiency in the other foot is an individual matter. Again, I warn against overtreatment. There are certain forms of therapy with which I am sure you are familiar, but I would be careful not to overtreat the other foot.

After something is done to one foot, there may be more strain upon the other. If a toe, or other part of a foot, or a knee joint is saved in one limb while the other foot is going bad, the problem of making the patient ambulatory with that other foot becomes greater.

Before I close this discussion on surgery, I should like to acquaint you with the thinking of vascular surgeons today. You have heard a great deal about removing atheromatous plaques from large arteries, grafting, and the progress made in the last few years.

Surgeons handling the problem of local thrombosis favor the excision of atheromatous plaques. The difficulty is in evaluating the patency of the arterial system below the thrombosis. In large arteries, such as the aorta and the iliac, excision of atheromatous plaques can be performed and arterial grafts successfully inserted.

The opinion of vascular surgeons is swinging toward grafts and away from excision of the intima, because the incidence of thromboses following the latter procedure has been high. With the excision technique, the intima is stripped off below. After the blood is turned back into such an artery, there is a much higher incidence of thrombosis than in the larger arteries.

MODERATOR KINSELL: We shall now consider some of the questions from the audience. Those that overlap will be grouped together.

One group concerns the questions of whether hyperglycemia without glycosuria should be treated, and what percentage of middle-aged or elderly diabetics can be managed with diet alone.

What is your opinion, Dr. Root?

DR. ROOT: If the patient has hyperglycemia because he has had diabetes for many years and has reached the stage where he has a high renal threshold, and if he is physically sound, free from fatigue, and free from complications, he should be treated. Patients over 60 years of age in whom diabetes is of recent development—these are the people who have mild diabetes—should be treated as they come to us, some of them with no complications. Taking the group as a whole, perhaps 30 or 40 per cent can be treated with diet alone.

MODERATOR KINSELL: As a corollary to that question, would Dr. Tolstoi, Dr. Pollack, or any member of the panel indicate the level of blood sugar that should be maintained—the point below which the level should not fall, regardless of the method of management—in an elderly diabetic patient with no obvious coronary artery disease.

DR. POLLACK: One thing must be remembered; there is a physiologic increase in the blood sugar concentration with age. Although textbooks state that the normal fasting blood sugar level is approximately 80 to 100 mg. per 100 ml. based upon the true blood sugar method, in elderly patients the statement does not hold. In them, it is common to find a blood sugar concentration of 130 or 140 mg. per 100 ml. The desirable blood sugar level in this group of people is difficult to determine. It is my practice not to worry if the postprandial level is between 180 and 200 mg. We do not attempt to bring the fasting level below 150 mg. in elderly diabetic patients for these reasons.

I should like to bring up a rather provocative point: that hypoglycemia occurs because of lack of control, just as does hyperglycemia.

Hypoglycemia is probably a much greater threat to elderly patients than is hyperglycemia. The commonest cause of death in diabetic patients in the surgical wards of our hospital is actually hypoglycemia, which has precipitated a vascular accident. If the handling of the diabetic patient postoperatively is overenthusiastic, and the issuance of insulin orders not carefully supervised, hypoglycemia with cerebral apoplexy is likely to occur. We have seen many fresh retinal hemorrhages appear immediately after a hypoglycemic episode.

In speaking of control, remember that it is not merely control of one phase—of the blood sugar level or the glycosuria—it is control of the over-all syndrome.

MODERATOR KINSELL: Thank you.

Dr. Graef, I think you have a question that relates to some aspects of this subject.

DR. GRAEF: I have this question: "Why do most persons with Kimmelstiel-Wilson syndrome have a low blood sugar level?" I wish I knew. There are exceptions to this general experience. In the past year, I have observed at least 3 persons in whom keto-acidosis and large insulin requirements (in excess of 40 units per day) complicated the course of classic nephropathy of the Kimmelstiel-Wilson type.

It is generally held that this disorder becomes manifest at the end of a long period of diabetes, and that clinical recognition is dependent upon the presence of large amounts of albumin in the urine, the classic picture of retinopathy,

edema, and hypertension. If simpler criteria, like albuminuria in the presence of retinopathy, and a syndrome which is not full-blown are accepted as establishing the presence of this nephropathy, the variants are observed earlier in the course of the disease. The insulin requirements may be similar to those of patients with neither the retinopathy nor the nephropathy.

It may be that the classic cases involve persons who, approaching later life and having had the disease for many years, achieve somewhat reduced insulin requirements as a part of the progression of the Kimmelstiel-Wilson phenomenon. Because of anorexia, they reduce their food intake, and to this extent diminish the challenge to their endogenous manufacture of insulin.

These factors may aid in explaining the widely noted, relatively small requirement for insulin in the average patient with Kimmelstiel-Wilson syndrome.

MODERATOR KINSELL: Has anyone else a comment bearing on that subject?

DR. TOLSTOI: I have observed, although infrequently, that when a patient has a full-blown Kimmelstiel-Wilson syndrome, the history may be as follows: "I used to take 50 or 80 units of insulin, and now I suffer shock on 30." The classic case emphasized in the literature is that reported by George Dana from Johns Hopkins Hospital. The patient had required something like 80 units of insulin, but near the time of death no insulin at all was required to keep the disease well controlled, according to their standards. This patient had the Kimmelstiel-Wilson kidney.

I wonder what Dr. Root's experience is?

DR. ROOT: I have seen the same thing. Several patients in the last stages have ceased to require insulin. I am just as puzzled by this as is everybody else.

It is important to remember that patients having Kimmelstiel-Wilson disease are not protected from diabetic coma. When ketosis develops, the problem of how much insulin to use arises. The patient with uremia is not resistant to insulin, whereas the patient in coma is. Disastrous accidents have occurred when too much insulin has been given to a patient who had ketosis and also failing kidneys with uremia. I am sure that is what Dr. Graef was talking about; everyone here has had that experience. Such an emergency occurs infrequently, but will be observed more often as the number of patients with Kimmelstiel-Wilson syndrome increases.

DR. POLLACK: In any protein-depleted individual, insulin requirements are diminished. In the Kimmelstiel-Wilson syndrome, as you know, there is marked protein-depletion. For these patients, nourishment from protein sources is minimized and at times completely eliminated. Thus, one of the main sources of blood sugar has been removed.

DR. TOLSTOI: We treated an elderly woman from about the age of 60 to age 72. She was insulin-resistant and required 750 units of insulin daily. Her glycosuria was disregarded. Her condition remained satisfactory. She died of a cerebral vascular accident. The postmortem examination showed no Kimmelstiel-Wilson lesions in the kidney. I wonder whether or not it is a corollary, that in an insulin-resistant person it can be predicted that no renal lesions will be found.

MODERATOR KINSELL: A few important questions remain. One has to do with

insulin. Perhaps Dr. Root would like to comment on the relative place of Lente as compared with NPH or protamine insulin.

DR. ROOT: In comparing results in children, we have found that with Lente insulin the duration of action and the blood sugar curve are practically the same as those observed with NPH, and not much different from those with protamine zinc insulin. Perhaps each is a little longer, but of about the same character.

"Is it pure?" Yes; Lente insulin contains no protein. Lente contains zinc and acetate (the buffer), but no protamine.

Difficulty regarding insulin reactions is probably no less with Lente than with NPH insulin.

MODERATOR KINSELL: Do any other members of the panel have any remarks about Lente?

DR. POLLACK: The situation with regard to local reactions is probably one of the main differences. With Lente, local reactions are not as pronounced as with NPH; on the other hand, the amount of local pain and burning is so much greater that many people object to it. The protamine zinc insulins are preserved with phenolic compounds or creosotes, which are not present in the Lente insulins. These phenolic compounds act as local anesthetics. That is probably one of the reasons why the Lente form causes more local burning, but less itching.

DR. MCGAVACK: If a patient who has had troublesome local reactions with zinc insulin is treated instead with Lente insulin, special care is necessary regarding the dosage, because there is hardening and fibrosis of the areas used as sites for injection. These fibrosing reactions usually do not occur with Lente, and therefore absorption is better. As a result, the requirement for Lente insulin will be somewhat less than that of the other form.

MODERATOR KINSELL: One question concerns the significance of serum beta-lipoprotein levels in diabetes. Do any of the panel members feel sufficiently well informed to give an opinion?

DR. ROOT: In our series, we determined serum lipoproteins by the Gothman technic. In blood samples obtained during diabetic coma or ketosis, the serum lipoprotein and cholesterol levels were increased.

A similar high level of serum lipoproteins is found in young patients with uncontrolled diabetes of long duration.

The elevation of lipoprotein concentration is a little more striking than that of cholesterol, so there is a great deal of interest in the lipoprotein group and in the sub-groups under that general heading.

Dr. Kinsell is really the one to talk about that.

MODERATOR KINSELL: Because of the short time remaining, I shall reply instead to a question on the advisability of substituting vegetable fat for animal fat in diabetes.

In a diabetic patient with hypercholesterolemia, serum cholesterol and phospholipid concentrations can be reduced to normal levels if significant amounts of vegetable fat are introduced into the diet, and animal fat excluded. Whether this is good, bad, or indifferent in a clinical sense, as far as vascular diseases are concerned, is still to be determined.

The mechanism is not clear as yet, but some recent observations suggest that the amount of unsaturated fatty acid in the vegetable fat may be a very important factor.

In recent years, the possible role of the liver and of hepatic dysfunction in diabetes has been scrutinized. No discussion of diabetes in elderly persons should be considered complete without mention of the role the liver may play in the over-all picture of the diabetic state.

Dr. McGavack, have you any comments?

DR. MCGAVACK: I think that in some elderly persons with diabetes, there is evidence of fatty disturbance in the liver. Probably, this is due to, or associated with some degree of pancreatic fibrosis. However, in most elderly diabetics, this change in the pancreas is subclinical and in this respect I see no reason for postulating a difference between younger and older diabetic subjects.

MODERATOR KINSELL: Does any member of the panel believe that a fatty liver in itself may be a factor in diabetes in the middle-aged as opposed to juveniles? If so, does any one believe that the use of so-called lipotropic agents has any place in the management of diabetes in the middle-aged?

Does any one wish to commit himself?

DR. ROOT: I'd like to commit myself to this extent: First, "Does dysfunction of the liver cause diabetes?" I know of no evidence that it does. Extensive testing of liver function in young people has not revealed the slightest suggestion of liver disease as a factor in the causation of diabetes.

When a fatty liver develops in a patient with diabetes, the picture may be altered in many ways. Some cirrhotic patients may become more resistant to insulin—some less. A patient with a fatty liver may not need insulin; he may have spontaneous hypoglycemia. The insulin requirement may vary over a wide range in the diabetic in whom liver complications have developed.

DR. GRAEF: I should like to add a word about the state of the aged patient who presents an enlarged liver as a part of the diabetic pattern, or as a finding on physical examination. This has no bearing on hepatic pathophysiology in relation to diabetes, but on the necessity for a highly individual approach to the patient's problem.

Control of the diabetes requires the physician's best efforts in assessing the patient's needs. This involves determining the energy requirements, both at work and at rest; the physiologic metabolic requirements regarding cardiocirculatory and respiratory performances; and the responses to stress, emotional factors, and infections. The elderly diabetic patient who presents evidence of a disturbance in protein or fat metabolism—and I assume that a fatty liver may be a sign of accumulation of fat in excess—needs control in the broader sense of the word. I am not referring merely to the use of insulin, but to an appraisal of his total nutritional state and of the functional state of all his organs.

DR. TOLSTOI: I do not know whether or not Dr. Root intended to say that the liver is not a causal factor in diabetes. I think that none of us is prepared at present to say that it is or is not.

Some work in progress hints rather strongly that the liver is involved. The

old overproduction theory of diabetes—that the liver runs away with itself and causes a good deal of glycogenolysis—has not yet been disproved. Soskin's work is on a fairly good foundation. Some recent work by Arthur Mirsky of Pittsburgh indicates that the liver is intimately connected with the diabetogenic mechanism. Those are high-sounding words, perhaps meaning little, but I want to convey the idea to you that the liver may be involved in the process. We ought to keep an open mind.

MODERATOR KINSELL: A problem that warrants discussion is the question of the desirability of a group, a clinic, or a public health type of approach to the management of diabetes as compared with the individual approach.

To begin, will each member of the panel express his opinion regarding the relative value of the two approaches.

DR. TOLSTOI: I think that each diabetic patient must be treated individually.

MODERATOR KINSELL: Do you think that an individual physician should attempt, without hospitalization, to standardize an average diabetic patient? Do you think the cause of optimal management of diabetes would be best served if every patient were first either hospitalized or followed by a group, with adequate dietetic care, in order to get him started in the right direction?

DR. TOLSTOI: I shall give my personal experience: I never hospitalized a diabetic patient unless there are complications such as an infection, any other serious medical condition, ketosis, or a combination of these.

In all instances in which the diabetic patient is ambulatory, the diabetes newly discovered or established, and a good many symptoms are present, I prefer office management rather than hospitalization.

DR. POLLACK: There are definite advantages to group education. I believe that a major problem in the management of diabetes is education of the patient. Obviously, the general practitioner in his private office does not have the time or patience to sit down and repeat verbatim the same instructions to each patient day after day. The process is time-consuming, and the patients cannot afford to pay for it.

Therefore, patient education is probably best handled on a group basis through technical assistants who have been trained in this type of teaching. Actual management should stay within the realm of the practitioner who knows the problems of the individual patient.

DR. ROOT: I agree with the basic principle that every diabetic patient needs his own doctor. The doctor-patient relationship is essential for success. I also agree that early patient education is important.

As for the community approach, we are interested in group teaching, and have been for many years. In Boston, we have a community approach through the Red Feather organization. A committee of 30 people is studying the problem in an effort to find out how to improve the situation of the diabetic patient through education, how to prevent the increasing incidence of blindness, and how to alleviate the problem of foot lesions. Last week a conference was held, to which six hospitals were invited to send personnel to confer about education of the diabetic. Seventy-five persons, including dietitians, social workers, doctors,

nurses, and hospital superintendents attended. The conference concluded that education for diabetic patients is sadly lacking in Boston. The committee is going to recommend that all hospitals have an official on the subject of patient education in general—not limited to the education of diabetics only. I believe that might well become a matter of general professional policy.

Physicians on the staff should cooperate in this venture. It should not be left to hospital superintendents and social workers.

DR. GRAEF: I suppose that we all practice both kinds of care, but that we give individual care to patients who can take our time and pay for it, whereas other patients receive group instruction, in clinics, directly or indirectly from physicians.

I often suspect that the private patient, because the physician is too busy, is deprived of the education that the clinic patient receives. The question of meeting the patient's need is a highly individual problem for the conscientious physician. It is time-consuming and tedious, but nothing is more rewarding than good management of diabetes, with prevention of the grievous complications within our cognizance and control.

DR. MCGAVACK: The two major approaches to education of the patient have been well delineated by the previous speakers. In addition to the measures outlined, we should not forget our clinical and lay diabetes societies. Such organizations in all communities could be encouraged to further education of the patient. If conscientiously carried out, and supported by physicians, as Dr. Root has suggested, the problem of teaching the patient might be solved.

DR. SMITH: Years ago, we organized in the Presbyterian Hospital in New York a combined surgical and medical service to treat diabetic patients that came to the hospital. It has been my experience generally that surgical diabetic patients do best when they are segregated and are seen regularly by a surgeon interested in the problem and by a medical man versed in diabetes. There is less morbidity, and the mortality is less.

MODERATOR KINSELL: I want to thank the panel for a most interesting and stimulating discussion, and the audience for excellent participation.

X-RAY THERAPY AS A POSSIBLE CAUSE OF THE SHOULDER-HAND SYNDROME

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Beginning with the description of causalgia, generally attributed to Weir Mitchell during the Civil War, a large number of similar clinical entities have been recognized. These have in common the occurrence of musculoskeletal pain, followed shortly by nonpitting edema and later by muscular atrophy and osteoporosis. The primary painful stimulus may be due to local trauma of the extremity, but it often arises from organs and tissues in other and distant parts of the body. The generic term "reflex sympathetic dystrophy" has been accepted for its descriptive function, as it suggests the most probable pathogenic mechanism. The shoulder-hand syndrome was first recognized as a distinct member of this group by Steinbrocker in 1947.

The purpose of this report is to call attention to the possibility that roentgen therapy to the shoulder, even in small doses, may be a primary stimulus in the series of events leading to development of the typical clinical picture. Although our suggestion is necessarily a tentative one, we feel that our experience is sufficiently striking that others should be alerted to this possible complication.

CLINICAL DESCRIPTION

The shoulder-hand syndrome usually occurs in patients of the older age group. It is most often unilateral, though it may be bilateral. Either the shoulder or the hand is affected first, or symptoms may appear in both simultaneously. Stiffness and moderate pain, becoming more severe on attempted motion, are common presenting complaints. The affected hand presents a uniform brawny edema with tense, shiny bluish skin. Although the patient may complain of pain radiating through the entire arm, the area of the elbow often remains singularly free of objective changes. Symptoms usually progress for three to six months, followed in many cases by atrophy of muscles and subcutaneous tissue and flexion deformities of the hand. Steinbrocker and his associates have presented a full clinical description and classification (1).

The shoulder-hand syndrome has been most frequently reported following myocardial infarction, but it has also followed such conditions as local trauma, infection or operative manipulation of a shoulder, hemiplegia, various abdominal operations, pneumonia, or vascular disease of the extremity. In many instances there is no apparent cause.

PATHOGENESIS

The mechanism by which the syndrome is produced remains obscure. The most widely accepted conjecture postulates a reflex arc, the afferent limb of which

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receives painful stimuli from visceral or ligamentous structures (2). These stimuli activate an "internuncial pool" of several spinal cord segments which then discharges through the motor neurones of either the sympathetic system or the anterior motor horn cells of the voluntary system, producing muscle spasm and the neurovascular and trophic changes that constitute the typical clinical features of the syndrome. For reasons poorly understood, this process becomes self-perpetuating, and impulses continue to be sent into the sympathetic pathways until checked by such measures as procaine infiltration, sympathectomy or rhizotomy. The frequent failure of these direct approaches to therapy as well as the success of treatment with corticotropin (ACTH) and cortisone (3) serve to confuse the issue further.

CASE REPORTS

Case 1: Mrs. A. W., a woman aged 61, was first seen at the Lynn Clinic on June 18, 1951. She complained of pain and stiffness in the right shoulder. Physical examination showed nothing abnormal except for limitation of motion at the shoulder. Neurologic findings were negative. Roentgenograms of the right shoulder showed a small amorphous calcification in the soft tissues at the site of insertion of the supraspinatus tendon. The adjacent bone was normal. The patient received three x-ray treatments between June 29 and July 2, 1951. Dosage factors were: 150 KVP, 20 m.a., distance 50 cm., filtration 0.75 Cu plus 1 mm Al. She received 150 r to anterior and posterior shoulder portals for a total of 450 r (air) to each port. The patient experienced complete relief of pain and disability, with only slight residual soreness. On July 20, 1951, about three weeks after completion of therapy, she returned complaining of moderate shoulder pain associated with swelling of the dorsum of the hand

FIG. 1. *Case 2.* Pre-treatment films showing small sliver of soft-tissue calcification but normal underlying bone.

and stiffness of the fingers. She thought the discomfort in the shoulder differed in character from the original complaint. With small doses of analgesics she improved gradually and was completely relieved by November 15, 1951. Another roentgenogram of the shoulder showed no change in the soft-tissue calcification or appearance of the underlying bone when compared with the pre-treatment examination.

Case 2: Mrs. M. M. This 38-year-old woman was first seen by us on May 14, 1951. She complained of pain and stiffness in her left shoulder. Except for limitation of motion in the affected joint, the results of physical examination were negative. Roentgenograms showed bilateral cervical ribs and a small fragment of calcium in the soft tissue adjacent to the head of the humerus (Fig. 1). The underlying bone was normal. X-ray therapy was given from June 6 to June 18, 1951, on alternate days for a total of five treatments of 150 r each. Dosage factors were the same as those used in Case 1. The patient experienced almost complete relief of pain during the period of treatment. She returned on June 26, 1951, however, complaining of swelling and inability to close her left hand. There was no discomfort at the shoulder. Under conservative treatment the edema gradually subsided during the subsequent six weeks. When she returned for examination of August 15, 1951, there was atrophy of the small muscles of the left hand, tightness of the skin and a slight flexion contracture. Roentgenograms of the shoulder now showed marked osteoporosis and atrophy of the bone. The soft-tissue calcification was no longer visible (Fig. 2). On September 17, ACTH therapy was initiated. The patient improved steadily during the subsequent eight weeks. Four months later she was free of symptoms and the skin changes were almost imperceptible.

Case 3: Mrs. A. N., aged 58, was first seen at the Lynn Clinic on October 20, 1954. She was complaining of pain in her right shoulder with stiffness and limitation of motion. Roentgenograms showed soft-tissue calcification adjacent to the head of the humerus. She received three x-ray treatments on alternate days and a fourth treatment after one week, each treatment being 150 r with the same dosage factors used in the previous cases. Pain was relieved

FIG. 2. *Case 2.* Advanced bone atrophy following roentgen therapy. This finding is typical of the shoulder-hand syndrome.

and the full range of motion restored. One month later she returned with swelling, pain and stiffness of the right hand. The skin over the affected part was tense and cyanotic. Repeated x-ray studies showed no change in the shoulder joint area. The patient's symptoms grew worse, and after two weeks there was definite atrophy in the small muscles of the hand. Treatment with cortisone was initiated at this time. Symptomatic improvement was noted in less than one week. After two months the patient had no complaints and all objective signs of her illness had disappeared. She has remained perfectly well to date.

DISCUSSION

In each of these cases, clinical features of the shoulder-hand syndrome followed the use of x-ray therapy for peritendinitis calcarea. We think that a cause-and-effect relationship can logically be suggested. The vascular changes that invariably follow roentgen therapy, even in very small dermatologic doses, may be an important intermediary factor. One may also speculate that many apparent failures in the roentgen therapy of peritendinitis calcarea are in fact complications of the treatment. The possibility that we have simply recorded a coincidence of manifestations must be admitted. Since roentgen therapy is frequently used for peritendinitis calcarea, we feel that others may wish to anticipate this problem. The observation of additional cases can determine whether this is a real complication and, if so, whether it occurs with sufficient frequency to make it a significant one.

SUMMARY

Three cases are reported, in each of which the shoulder-hand syndrome appeared three to four weeks after x-ray treatment for peritendinitis calcarea at the shoulder. It is suggested that x-ray therapy may have precipitated reflex sympathetic dystrophy in these patients.

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PROBLEMS OF SEDATION IN THE ELDERLY

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The restless, noisy or confused old patient commonly presents a difficult problem in management, both in his own home as well as under hospital conditions. So much indeed is this so, that a survey of reasons preventing normal home care in any unselected group of elderly patients is likely to show one of these mental symptoms as the prime factor, necessitating special attention, particularly at night. A satisfactory therapeutic approach to this interrelated group of symptoms is therefore essential if older people are to be nursed at home during acute or terminal illnesses.

The group of medical conditions underlying the symptom-complex of mental disturbance is a large one, ranging from a simple febrile state, through drug intoxications of a minor or major degree, to grave functional or organic cerebral disturbances. The treatment indicated consequently varies from such simple measures as attending to physical comfort, or discontinuing the offending drug, to heavy sedation with powerful agents. It will therefore be readily understood that the treatment of confusion and restlessness should depend on a thorough knowledge of its origin, and that sedation before the cause is discovered is a procedure as unscientific as the masking of a severe abdominal pain with an injection of morphine.

The ensuing table lists some of the more common causes of restlessness and confusion in an elderly subject. In interpreting it, it must be understood that in old age, as well as in early childhood, the border-line between lucidity and confusion is a narrow one, easily crossed either way. Just as a brief incident of "lightheadedness" in early life should be viewed without undue alarm, so relatives and attendants should look on temporary confusion in the aged as no reason for panic.

Causes of Confusion in the Elderly

1. Nervous agitation.
2. Bodily discomfort, from inactivity, pain, thirst, overheating, rectal and vesical distention.
3. Metabolic upsets, fever, toxaemia, blood-electrolyte disturbance, hypovitaminosis.
4. Functional and organic cerebral states: cerebral congestion and anaemia; cerebro-vascular accidents; abscess or tumour; meningitis.
5. Drug intoxications, acute or cumulative: for example, from bromides, barbiturates, morphine derivatives, hyoscine, sulfonamides.

Added factors obscuring diagnosis are lowered perceptive powers in old people, especially for pain, and their difficulty in self-expression when mental deterioration has set in.

When a problem of such a nature is approached, the first step should be inter-

rogation of the patient in an endeavour to list his symptoms and to find any site of discomfort. Nurses and attendants should also be asked as to sedation or other treatment given in the preceding hours. Reports as to normal bowel and bladder function should not be accepted without question. A brief physical examination should now be made, special attention being paid to the condition of the skin for indication of overheating, and to the abdomen for detection of a distended bladder. In all cases, a digital examination of the rectum is required, in view of the frequency of silent overloading. Signs of congestive heart failure, distended neck veins, basal lung crepitations, a tender enlarged liver and oedema of the dependent parts may point to a coincidental cerebral congestion as the cause of the disturbance. A superficial neurologic examination may indicate an intracranial cause, but quite extensive cerebral lesions may fail to produce physical signs in the elderly. If the patient is known to have been taking bromides, even in therapeutic doses, or if he has been admitted to hospital without evidence on this point, it will be wiser to take blood for estimation of the serum bromide level.

This examination alone will frequently disclose the cause of restlessness and indicate an effective line of therapy, which either alone or with a mild sedative, will restore peace and tranquillity. Pain and discomfort relieved, a distended bladder decompressed by a catheter, and an overloaded rectum relieved by an enema (though sometimes a manual removal of impacted faeces may be needed), the patient should relax into quiet sleep. When a congested brain accompanies heart failure, injection of a mercurial diuretic may work wonders, whereas a strong hypnotic will be useless; whence the saying that mersalyl is the best sedative in heart failure.

Such measures do not always work, however: either no cause is discoverable, or the apparently correct measures are instituted without the confusion or restlessness being abolished. In such cases "blind" sedation will be necessary. In other cases, the condition indicates that sedation is the correct immediate form of treatment. The problem before us now is to secure the maximum sedative effect, with the minimal dose of safe hypnotic. It is best approached on the assumption that the barbiturate group of drugs are unreliable with elderly people, and are sometimes frankly dangerous, because of their tendency to precipitate or increase confusion, either from their immediate, or from a cumulative effect; other therapeutic substances are therefore to be preferred. For this reason, the barbiturates are relegated last in order of consideration. Bromides should not be used in sedation of this type; in old people, they are uncertain in action, being frequently ineffective. They have a marked tendency to accumulate in the cerebral tissues, thus increasing the confusion that they are supposed to relieve. If undetected bromide intoxication already exists, further administration of the salt may be fatal.

Sedatives

Sedatives may be considered in the following order:

1. *Aspirin with Pulv. Ipecac. Co.* (*Dover's Powder*). This old-fashioned combina-

tion is simple, frequently effective, and cheap. It is especially valuable in the presence of pain.

2. *Alcohol* is a most effective sedative in the aged, and usually very acceptable to the patient. It should be given in full dosage, either as a double whisky, brandy or rum. Its effect in potentiating certain other hypnotics must be remembered. It is dangerous in combination with barbiturates, the toxicity of which it seems to enhance, and it should be used with care if chloral is also given.

3. *Chloral Hydrate and Syrup of Chloral.* These most valuable preparations have unfortunately largely dropped out of fashion, having been banished nearly thirty years ago by the earlier barbiturates. They are only now staging a "comeback" in geriatrics. As a routine sedative, two capsules (7½ grains each) of chloral hydrate may be adequate, but for more severe restlessness of sudden onset, three capsules will be required. The corresponding dose of syrup of chloral is 2 drams, well diluted with an aromatic water such as aq. menth. pip. Sleep is generally sound, and the patient wakes refreshed. Chloral is said to be a cardiac depressant, and should therefore be avoided if there is severe cardiac weakness. The potentiating effect of alcohol on chloral should be remembered; a combination of chloral hydrate with alcohol is said to be the basis of the "knock-out drops" or Mickey Finn of the underworld.

4. *Methyl Pentynol* (Dormison) is a mild, reliable, quickly excreted sedative, with few side-effects, and is ideal for an agitated patient not actually suffering pain. The normal dose is two to five capsules (250 mg. each), or 2 to 5 drams of the elixir. Dormison is compatible with alcohol. (In Great Britain, methyl pentynol is known as Oblivon.)

5. *Doriden* (Ciba) is a rapid-action, non-cumulative hypnotic, having the formula α-phenyl-α-ethyl glutarimide. The normal dose is one to two 0.25-Gm. tablets. Not infrequently Doriden may produce a morbelliform or rubelliform skin rash which may be highly irritant. The pruritis is controllable with antihistaminic drugs, and the rash fades rapidly when the cause is withdrawn. In other cases, Doriden can be considered as reliable and effective.

Barbiturates. The position of the barbiturate group in sedation can now be considered. Elderly patients will commonly be met who regularly use these drugs for their hypnotic effect, with no apparent harm. Under these circumstances, it may be wise to allow continuance of the drug, provided there is a close watch for side-effects. Even so, a metabolic or organic upset may completely alter the hypnotic's action. For example, a febrile illness such as pneumonia, or the after-effects of a small cerebral thrombosis, may cause the barbiturate to induce a confusional reaction in which the patient may fall out of bed, whereas previously its effect had been quite satisfactory. In such cases, any future administration may lead to a repetition of restlessness or disorientation. In the writer's experience, it is always wiser to do without this group of drugs in aging patients.

When the foregoing methods have been tried without success, or when it is judged that the restlessness is so great that milder forms of sedation are likely to be inadequate, a more vigorous approach must be taken. In such circumstances, paraldehyde is the agent of choice.

Paraldehyde can be administered orally, as a rectal infusion or by intramuscular injection. Its extremely offensive taste and the technical difficulties of the rectal route in an uncooperative patient make the injection method preferable. The effective intramuscular dose is 5–8 ml. The solution is self-sterilizing and non-irritant if injected deeply into the buttock or the outer aspect of the thigh. Because paraldehyde decomposes in the presence of light and air into pure glacial acetic acid, it should never be administered from a ward stock bottle, by any route, but only from sterile ampoules of 5–10 ml. size, or from 1-ounce actinic glass bottles, with ground-glass stoppers. Massive rectal necrosis has resulted from the infusion of deteriorated solutions, and old stock has also been known to produce sterile abscesses in muscle. Given from ampoules as described, paraldehyde is both safe and effective. When sedation begins to pass off, in six to eight hours, a further injection of 4 ml. may be given. Paraldehyde is fully compatible with alcohol. Excreted through the breath, it may act as a lung irritant and should be used with caution in broncho-pulmonary infections.

Morphia and Hyoscine. When both mild hypnotics and paraldehyde prove ineffective, as at times they do, the much less safe morphia and hyoscine, either alone or in combination, must be considered. Hyoscine is uncertain in its effect and may even accentuate restlessness. Morphine, which is at its best in the presence of pain, or in the distress incidental to heart failure and cardiac asthma, may lead to troublesome vomiting. Cases of extreme restlessness and uncontrollable noisiness, untouched by the less powerful sedatives, are often caused by major intracranial disturbances, such as cerebral haemorrhage, the prognosis of which is already grave. To produce quietness in such a case, a combination of morphine (gr. ¼ to gr. ⅓) with hyoscine (gr. $\frac{1}{100}$ to gr. $\frac{1}{75}$) may be required. The margin of safety between the effective and the lethal dose is very narrow, and a difficult choice has sometimes to be made between risking what may prove to be an overdose, and allowing the patient to die from exhaustion, and to distress his entire neighbourhood in so doing. In such cases, it is wise to put the position to the relatives and to seek their cooperation.

Tranquillizing Drugs

The introduction of "tranquillizing" drugs into modern medicine has had little influence on the handling of the *acutely* confused, disorientated patient. In cases of persistent confusion and restlessness due to bodily distress they may furnish considerable help in preventing acute exacerbations of restlessness.

Chlorpromazine is often effective in lessening anxiety and nervous tension, and many restless, confused patients who manifest these two features derive great benefit from even such small doses as 10 mg. thrice daily. Nocturnal "cruisers" are sometimes more controllable if a suppository of 100 mg. is inserted rectally during the late afternoon. The drug enhances the effect of other sedatives and analgesics and is of particular value in the management of patients having inoperable cancer with severe pain or other distress.

The Rauwolfia alkaloids are gradually finding a similar place in geriatric sedation. Their value seems to lie in diminishing the tension state, from which rest-

less confusion develops, and in potentiating other sedatives which would be ineffective if given alone. On account of the apparent tendency of the single alkaloid, reserpine, to induce mood swings, with the risk of suicidal attempts, it is probably wiser to use a combination of alkaloids, such as Rauwiloid. Mental dullness the following morning can be countered by the use of an analeptic such as Ritalin (Ciba) or Meratran(Merrell), so that the patient can occupy himself normally during the daylight hours.

A FIVE-YEAR PROGNOSTIC STUDY OF ACUTE MYOCARDIAL INFARCTION

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In an effort to increase the life span of patients who have survived an acute myocardial infarction, various drugs and surgical procedures have been advocated. Attempts are being made to improve the survival time by continuous long-term anticoagulant therapy (1, 2), estrogenic substances (3, 4), heparin (5), diet (6), and surgery (7). As a control, long-term studies of persons who survived a myocardial infarction but who did not subsequently receive any special type of therapy should have value. We recently reported such a ten-year study (8). However, since the period of preventative treatment by the foregoing agents has been comparatively short, a five-year study would be of more current interest. We had previously made a five-year study on only 151 patients (9).

CLINICAL STUDY

The selection of patients was the same as mentioned in our preceding studies. Only those patients were included who had recovered from their presumed first myocardial infarction and who had lived more than two months. All the cases were seen in private practice. Only patients with characteristic clinical and electrocardiographic evidence were selected and those in whom the onset of the infarction could be determined with certainty. None received any special long-term or surgical therapy.

A total of 679 patients met the foregoing criteria. The period during which myocardial infarction had its onset ranged from January 1, 1940 to July 1, 1951, and the patients were followed until July 1, 1956. Only 26 or 3.8 per cent were lost to follow-up. A total of 653 patients were then available for analysis.

Table 1 shows the course of the 653 cases with respect to five-year survival, analyzed according to sex. The ratio of men to women was 5:1. Of the 653 patients, 229 or 35.1 per cent lived five years or less. Approximately an equal percentage of men and of women died within five years. There are only a few similar five-year studies in the literature. Table 2 is a summary of the available five-year survival rates. Bland and White (10) studied 162 patients who survived their first attack for at least one month. At the end of five years, 50 per cent had died. Smith (11) reported that of 85 patients who survived one month, 34 per cent had died at the end of five years. Cole, Singian and Katz (12), with an 80 per cent follow-up of 356 patients who survived at least two months after their first infarction (285 cases finally analyzed), reported that a third had died by the end of the fifth year. Eckerström (13) reported that of 98 patients who survived two months, 66 per cent were dead within five years. In some studies on long-term survival the data

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TABLE 1

Five-Year Survival Rate in 653 Patients with Acute Myocardial Infarction—Sex Distribution

	Died Within 5 Years		Survived 5 Years	
	Number	Per Cent	Number	Per Cent
Male	187	34.6	354	65.4
Female	42	37.5	70	62.5
Total	229	35.1	424	64.9

TABLE 2

Summary of Five-Year Mortality Data in the Literature

Author	Immediate Survival Time	No. of Patients	Per Cent Died
Bland and White (10)	1 mo.	162	50
Smith (11)	1 mo.	85	34
Cole *et al.* (12)	2 mos.	285	33
Eckerström (13)	2 mos.	98	66
Weiss	2 mos.	653	35.1

are not comparable with those in this report. Billings *et al.* (14) found that 55 per cent of 143 patients who survived a month were dead at the end of five years, but not all were studied in the first attack. Achor *et al.* (15) analyzed the clinical records of 250 necropsies in which the heart showed gross myocardial scars indicative of healed infarction. Of 108 patients whose myocardial infarction was diagnosed clinically, 76 per cent died within five years. Thus, the reported mortality comparable to the mortality in this study ranged from 33 to 66 per cent.

Table 3 shows the duration of life by years of the 229 patients who died within five years. Most of the deaths (70 per cent) occurred within the first three years. This has been previously observed (10, 15). However, it is impossible to predict when death will take place.

Table 4 is an analysis of survival, according to the sex and age of the patient at the time of onset of the myocardial infarction. The number of people of both sexes who lived longer than five years after an infarction was greater in the younger groups than in patients whose age at the time of the infarction was 60 years or beyond. This is to be expected and has been mentioned in all reports.

The cause of death was known in 214 cases; it was cardiovascular disease in 82 per cent. This is in accord with all other reports. The exact incidence of death from another myocardial infarction could not be determined, since many patients did not live long enough in their final illness to have electrocardiographic examinations. The types of cardiac deaths following a myocardial infarction have been well documented by others (15).

Rehabilitation after a myocardial infarct, and the functional status of the heart in relation to the prognosis, have been previously discussed (8, 9, 16) and will not be commented on in this report.

The number of patients in this series who had diabetes were so few that the

TABLE 3

Duration of Life After Acute Myocardial Infarction

Period (yrs.)	No. of Patients Who Died Within 5 Years		
	Male	Female	Total
0–1	54	10	64
1–2	42	9	51
2–3	40	9	49
3–4	28	5	33
4–5	23	9	32
Totals	187	42	229

TABLE 4

Analysis of Survival, According to Sex and Age of the Patient at Time of Onset of Acute Myocardial Infarction

Age (yrs.)	Died Within 5 Years			Survived 5 Years		
	Male	Female	Total	Male	Female	Total
>–30	0	0	0	1	0	1
30–39	10	0	10	24	0	24
40–49	35	1	36	81	6	87
50–59	64	13	77	148	18	166
60–69	61	15	76	81	32	113
70–79	15	11	26	17	11	28
80+	2	2	4	2	3	5
Totals	187	42	229	354	70	424

data relative to diabetes had no statistical significance. Bradley and Bryfogle (17) found that 62.5 per cent of 32 diabetics who survived two months after their first myocardial infarction lived less than five years.

SUMMARY

A five-year follow-up study was made of 653 patients who lived more than two months after their first myocardial infarction.

Of these, 35.1 per cent lived five years or less.

Approximately an equal percentage of men and of women died within five years.

Most deaths occurred within the first three years.

Following acute myocardial infarction, the number of people of both sexes who lived more than five years was greater in the younger than in the older age groups.

The major cause of death was cardiovascular disease.

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COMPARISON OF RESULTS OF BILIARY-TRACT OPERATIONS IN OLDER AND YOUNGER PATIENTS

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In order to investigate the results of biliary-tract operations in older and younger persons, an analysis was made of data from the hospital records of 500 patients who underwent such operations at the Jameson Memorial Hospital, New Castle, Pennsylvania, during the years 1943–1952 (1). A follow-up study was made through the use of a questionnaire sent to surviving patients.

AGE AND SEX DISTRIBUTION

In this analysis, data on 107 patients age 60 years or older (Group I) were compared with those on 393 patients who were less than 60 years of age (Group II). The ratio of men to women was 1 to 4 in Group I, and 1 to 5 in Group II. Table 1 shows the age and sex distribution of the patients in Group I.

Besides acute and chronic cholecystitis, conditions not related to the biliary tract existed in many patients. Twenty-nine per cent of those in Group I were affected, as compared with 19 per cent in Group II. The concomitant conditions present in these elderly subjects included the following: hypertension, 9; arteriosclerotic heart disease, 1; diabetes mellitus, 4; cirrhosis of the liver, 3; cancer of the pancreas, 2; cancer of the prostate, 1; prostatic hypertrophy, 1; arthritis, 2; Ménière's disease, 2; duodenal ulcer, 2; regional ileitis, 1; epigastric hernia, 1; nephritis, 1; and involutional melancholia, 1.

OPERATIVE PROCEDURES

Table 2 lists the operative procedures. Cholecystectomy was performed in a somewhat lesser proportion of Group I than of Group II patients, but cholecystotomy and choledochotomy were performed in a substantially larger proportion of Group I patients. The bile ducts were explored at the time of cholecystectomy or cholecystotomy in 11 patients of Group I and in 12 patients of Group II. Choledochotomy was the only operation in 2 elderly patients and in 10 younger patients who had previously undergone cholecystectomy or cholecystotomy.

Jaundice was present in 14 (13 per cent) of the patients in Group I and in 25 (6 per cent) of patients in Group II.

FINDINGS AT OPERATION

Pathology reports

The pathologic examination of gallbladders removed at operation confirmed the presence of chronic cholecystitis in equivalent percentages of the older and younger patients (Table 3). Subacute cholecystitis also was found in the same percentage of patients in the two groups. Acute cholecystitis occurred in four

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TABLE 1

Age and Sex Distribution of Patients 60 years of Age and Older

Age (yrs.)	No. of Patients	No. of Men	No. of Women
60–69	78 (73%)	12	66
70–79	27 (25%)	9	18
80–87	2 (2%)	1	1
Total	107 (100%)	22 (21%)	85 (79%)

TABLE 2

Surgical Procedures in 500 Patients

Surgical procedure	107 Patients 60 Years of Age and Older		393 Patients Less Than 60 Years of Age	
	No.	Per Cent	No.	Per Cent
Biliary Tract				
Cholecystectomy	92	86	363	92
Cholecystotomy	13	12	20	5
Choledochotomy as the only operation	2	2	10	3
Choledochotomy combined with cholecystectomy or cholecystotomy	(11)		(12)	
Other				
Appendectomy	44	41	209	53
Various	10	9	40	10

times as great a proportion of the elderly patients as of the younger. Normal gallbladders were removed from a lower proportion of the elderly patients.

Gallstones

Among patients who had either a cholecystectomy or cholecystotomy, gallstones were found in 84 per cent of those who belonged to Group I, and in 76 per cent of those who belonged to Group II. Table 4 compares the incidence of multiple and of single stones in the two groups.

Common-duct stones

The common bile duct was explored in 13 patients of Group I, 10 of whom had jaundice at the time of operation. Among Group II patients, the common duct was explored 22 times; 14 of these patients had jaundice. The incidence of stones in the patients undergoing this procedure is shown in Table 5. In the older group, a higher percentage of patients with jaundice had common-duct stones than in the younger group. The reverse, however, was true for patients without jaundice.

Confirmation of roentgenographic diagnosis

Reports of roentgenographic examination of the gallbladder were available for 50 of the Group I patients and for 168 of those in Group II. Table 6 summa-

TABLE 3

Pathology Reports on Patients Who Underwent Cholecystectomy

Pathology Report	92 Patients 60 Years of Age and Older	363 Patients Less Than 60 Years of Age
Chronic cholecystitis	81 (88%)	315 (87%)
Subacute cholecystitis	2 (2%)	7 (2%)
Acute cholecystitis	7 (8%)	7 (2%)
Normal gallbladder	2 (2%)	15 (4%)
No report	—	19 (5%)

TABLE 4

Gallstones Found at Cholecystectomy or Cholecystotomy

Gallstones	105 Patients 60 Years of Age and Older	383 Patients Less than 60 Years of Age
Multiple	69 (66%)	237 (62%)
Single	19 (18%)	52 (14%)
Totals	88 (84%)	289 (76%)

TABLE 5

Incidence of Common-Duct Stones in Patients With and Without Jaundice Undergoing Choledochotomy—Alone or Combined with Cholecystectomy or Cholecystotomy

	Patients 60 Years of Age and Older				Patients Less Than 60 Years of Age			
	With Jaundice		Without Jaundice		With Jaundice		Without Jaundice	
	10		3		14		8	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
Common-duct stones	6	60	1	33	6	43	5	62
No stones	4	40	2	67	8	57	3	38

rizes the findings. Stones were visible in the films of 40 per cent of the patients in Group I, and in the films of 57 per cent of the patients in Group II.

The extent to which the roentgenographic evidence of stones was confirmed by the pathology reports is shown in Table 7. The presence of stones was verified at operation in all of the patients in Group I who had *functioning* or *nonfunctioning gallbladders with stones* demonstrated roentgenographically. In 1 patient there was carcinoma of the common bile duct and of the liver, in addition to many stones in the gallbladder. In another patient, a diagnosis of functioning gallbladder with papilloma was confirmed at operation.

Among Group II patients, only 3 of 46 in whom the roentgenographic diagnosis *was nonfunctioning gallbladder with stones* had no stones at operation, so that this diagnosis was 93 per cent accurate. Similarly, only 3 of 50 patients in whom the roentgenographic diagnosis was *functioning gallbladder with stones* had no stones at operation (94 per cent verification).

TABLE 6

Findings on Roentgenographic Examination of the Gallbladder in 218 Patients

Condition of Gallbladder	Patients 60 Years of Age and Older		Patients Less Than 60 Years of Age	
	No.	Per Cent	No.	Per cent
Nonfunctioning, with stones	12	24	46	27
Functioning, with stones	8	16	50	30
Nonfunctioning; no evidence of stones	22	44	50	30
Poorly functioning	3	6	10	6
Normal	3	6	10	6
No diagnosis (plain film of gallbladder area)	2	4	2	1
Totals	50	100	168	100

TABLE 7

Correlation of Roentgenographic Visualization of Gallstones with Pathology Reports

Roentgenographic Diagnosis of Gallbladder Condition	Patients 60 Years of Age and Older			Patients Less Than 60 Years of Age		
	No. of Patients	Presence or absence of stones confirmed on pathologic examination	Per cent verified	No. of patients	Presence or absence of stones confirmed on pathologic examination	Per cent verified
Nonfunctioning, with stones	12	12	100	46	43	93
Functioning, with stones	8	8	100	50	47	94
Nonfunctioning; no evidence of stones	22	6	27	50	3	6
Poorly functioning; no evidence of stones	3	1	33	10	8	80
Normal gallbladder	3	2	66	10	8	80

When the roentgenographic diagnosis was *nonfunctioning gallbladder without stones*, however, stones were found at operation in 16 of 22 patients in Group I and in 47 of 50 patients in Group II, so that the roentgenograms were only 27 per cent and 6 per cent accurate, respectively, in these instances. One of the elderly patients with stones also had carcinoma of the head of the pancreas.

A roentgenographic diagnosis of *poorly functioning gallbladder; no evidence of stones* was made in 3 of the patients in Group I. At operation, 2 of them had a chronically inflamed gallbladder, with single and multiple stones, respectively; the third patient underwent gallbladder drainage without the finding of stones (33 per cent verification). In 10 Group II patients this roentgenographic diagnosis was made. In 2 of them operation revealed a gallbladder that was chronically inflamed and contained stones; in 2 the gallbladder was chronically inflamed but contained no stones; in 2 there was slight chronic inflammation; in 1 there was cholesterolosis; and in 2 the gallbladder was reported to be normal by the pathologist (80 per cent verification).

TABLE 8

Postoperative Complications

Complication	No. Among 107 Patients 60 Years of Age and Older	No. Among 393 Patients Less than 60 Years of Age
Thrombus, leg vessel	3	12
Pulmonary embolus	3	4
Cardiac conditions	4	4
Rupture of abdominal wound	2	2
Infection of operative wound	1	4
Peritonitis	1	1
Pneumonia	1	2
Total	15 (14%)	29 (7.4%)

TABLE 9

Results of Follow-Up Study

Report Concerning Improvement After Operation	Patients 60 Years of Age and Older		Patients Less Than 60 Years of Age	
	No. of replies	Per Cent replies	No. of Replies	Per Cent Replies
Better	53	87	225	90
No better	6	10	9	4
Worse	0	0	13	5
Death	2	3	3	1
Totals	61	100	250	100

The pathology report confirmed the roentgenographic diagnosis of *normal gallbladder* in 2 of 3 patients in Group I; in the third, the gallbladder was chronically inflamed and contained many stones. Among Group II patients, the roentgenographic diagnosis of normal gallbladder was made in 10. At operation, the gallbladder proved to be normal in 4 patients and abnormal in 6. Of the 6 abnormal gallbladders, all were chronically inflamed, in 3 there were no stones, 2 contained single stones, and 1 contained a papilloma.

POSTOPERATIVE COURSE

Operative mortality.

Eight patients (7.5 per cent) among those in Group I died postoperatively, and 12 (3.1 per cent) among those in Group II.

The cause of death in 2 women was *coronary occlusion*, which occurred eleven and twenty-two days after operation, respectively. One of these women, aged 68 years, had undergone removal of a chronically inflamed gallbladder with many stones and an appendectomy. The second, aged 65 years, had a stormy course with uncontrolled vomiting after gallbladder drainage and the removal of many stones.

A fatal *pulmonary embolus* occurred in a 74-year-old man who died twenty

days after a chronically inflamed gallbladder with many stones had been removed. At operation, a perforated duodenal ulcer that had recently become sealed was noted.

Another Group I patient died of *peritonitis.* This 64-year-old woman had undergone cholecystectomy and ileocolostomy for regional ileitis.

Hemorrhage from the liver caused the death of a 64-year-old woman, in whom reopening of the incision and exploration had to be performed twenty-eight days after cholecystectomy.

A 76-year-old, mildly jaundiced woman, desperately ill, toxic, and mentally confused at the time of cholecystotomy and attempted removal of common and hepatic duct stones, died from *shock* postoperatively.

Arteriolar nephrosclerosis caused the death of a 76-year-old woman with diabetes mellitus who also had jaundice. She had previously undergone cholecystotomy. The common duct was explored and a stone removed. The kidneys stopped functioning in this patient and she died two days after operation.

A 74-year-old man with *cancer of the pancreas* died on the twenty-eighth postoperative day. This man had had jaundice. Exploration of the common duct and cholecystectomy had revealed no stones.

The causes of death enumerated are those in the patients of Group I. It can be seen that the majority of the elderly patients in this group tolerated well the surgical procedures performed on the biliary tract.

Postoperative complications

The older patients remained in the hospital postoperatively an average of 17.4 days, and the younger patients 13.9 days.

When the incidence of postoperative complications in the older group could be compared with that in the younger group, it was found to be higher in the older patients. In Table 8 are listed the comparable complications in the two groups. Embolic or thrombotic episodes occurred in 6 patients (6 per cent) of Group I and in 16 patients (4 per cent) of Group II. The cardiac complications proved fatal to 2 patients in the older group with coronary occlusion, as mentioned under Operative Mortality. Nonfatal auricular fibrillation occurred postoperatively in 2 other patients of Group I. A fatal case of pulmonary embolus and a fatal case of peritonitis in Group I have also been mentioned previously. None of the 4 younger patients with cardiac conditions died as a result of these complications.

The hospital records showed additional complications in the patients of Group I. The following occurred postoperatively in 1 patient each: prolonged coughing, long period of bile drainage, hemorrhage from the liver, accidental opening of the duodenum at the time of operation, uremia, nonfunctioning kidneys, prostatitis that required transurethral resection, anemia, postoperative shock, and slow wound healing with watery discharge (in a patient with an inflamed pancreas).

FOLLOW-UP STUDY

To determine the effects of biliary-tract surgery on these patients, questionnaires were sent to the 480 survivors. The interval from the time of operation to

the time of replying to the questionnaire ranged from eight months to nine years. Replies were received from 65 per cent of the patients in both groups who survived the operative procedures, that is, from 61 (62 per cent) of the 99 patients remaining in Group I, and from 250 (66 per cent) of the 381 patients remaining in Group II. The responses of the older patients are compared with those of the younger patients in Table 9.

The proportion of patients who experienced improvement following operation on the biliary tract was approximately the same in each group—87 per cent of those in Group I and 90 per cent of those in Group II who replied to the questionnaire. However, 9 (17 per cent) of the Group I patients and 46 (20 per cent) of the Group II patients who said they were better reported that they still had some complaint. The older patients mentioned the following: pain similar to that prior to operation, constipation, pyrosis, epigastric distress, pain or hernia at the site of the incision, and numbness in the foot and leg.

Ten per cent of Group I patients and 4 per cent of Group II patients replying to the questionnaire reported no improvement. These patients also had various complaints, such as pain similar to that prior to surgery, pain at the site of the incision, gastric distress, and constipation.

None of the older patients reported feeling worse after surgery, but 5 per cent of the younger patients who replied said they were worse.

Two (3 per cent) of the Group I questionnaires and 3 (1 per cent) of Group II questionnaires were returned with the information that death had occurred. Of the 2 in Group I, 1 patient had died at age 69 of nephritis, six years following cholecystectomy. The other had died at age 65, one month after discharge from the hospital where she had undergone cholecystectomy. Postoperatively, this patient had had thrombophlebitis of the left leg and was discharged on the thirty-fifth postoperative day.

SUMMARY

An analysis has been made of data from hospital records of 107 patients aged 60 years or older (Group I) and of 393 patients less than 60 years of age (Group II) subjected to biliary-tract surgery over a nine-year period. A follow-up study was made through the use of a questionnaire.

Group I was characterized by a slightly lower ratio of female to male patients, a higher incidence of concomitant disorders, and an incidence of preoperative jaundice more than twice that in Group II.

Cholecystectomy was performed in a somewhat lower proportion of the patients in Group I than in Group II. However, cholecystotomy and choledochotomy were performed in a substantially greater proportion of Group I patients. Appendectomy was performed at the time of biliary-tract surgery in a lower percentage of the older patients. Approximately the same percentage of the older and younger groups underwent various additional surgical procedures.

The older patients had a greater incidence of acute cholecystitis. A normal gallbladder was removed from relatively fewer of the older patients. Almost the same proportion of older and younger patients had chronic cholecystitis. The incidence of multiple and single gallstones was greater in Group I patients, as

was the incidence of common-duct stones in jaundiced patients in whom the ducts were explored.

Nonfunctioning gallbladder without evidence of stones was the roentgenographic diagnosis in a greater percentage of Group I patients; at operation, however, stones were found in relatively more Group II patients. In general, the discrepancies between roentgenographic diagnoses and operative findings were less in Group II.

The mortality rate among Group I patients following surgery was almost two and a half times greater than among Group II patients. Postoperative complications occurred twice as frequently among Group I patients.

Follow-up study showed that an approximately equal percentage of patients from each group stated that they were better following biliary-tract surgery. However, residual complaints were more common in Group II. A greater proportion of Group I patients reported no improvement following the operation. No patient in Group I felt worse, but 5 per cent of the younger patients (Group II) reported that they were worse. Death had occurred in 3 per cent of the older patients and in 1 per cent of the younger group.

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FOOD CONSUMPTION OF "OLDER" FAMILIES*

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In a study of food consumption in Everett, Washington, conducted in the fall of 1953, the families in the sample were classified in a way which roughly corresponded to the stage in the family life-cycle. The "older" families—27 households consisting of adults all 50 years of age or older—were singled out for special study because of the growing interest in problems of this section of the population. The results are presented here.

METHOD OF SELECTION

First a cross-section sample of 226 households was drawn for the purpose of interviewing homemakers regarding the use of certain common foods. At that interview all homemakers who were willing to cooperate were asked to keep a daily record during the following week, of menus for meals and snacks at home and also for meals and snacks eaten away from home by family members. At the end of the specified week the interviewer called, picked up the menu forms, and filled out a detailed check-list showing amounts and prices of all food supplies used in the home menus. Amounts reported as fed to pets, thrown out, given away, or not used up, were deducted.

The sample of 226 households was a systematic random one drawn from addresses in a city directory, corrected for omissions, and supplemented by a list of new dwelling units. It satisfactorily represented all eligible households, that is, all those which included at least 2 persons who, during the week before the interview, had had half or more of their meals at home. Forty-seven of the households consisted wholly of adults aged 50 or over, and 27 of such "older" families furnished menus and food check-lists for the following week. Compared with the larger group of 47 families, these 27 included a somewhat greater proportion of households in which the head was 65 years of age or over and the homemaker 60 or over; a slightly greater proportion (5 per cent more) with incomes (after income tax) under $2000; and a slightly smaller proportion (5 per cent less) with incomes above $2000.

THE FAMILIES

All of the 27 families whose diets will be described consisted of 2 persons and all but 2 families were married couples. Fourteen heads and 11 homemakers were 65 years of age or over; none of the homemakers was employed outside

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TABLE 1

Nutritive value (per nutrition unit per day) of the food supplies in home meals during one week*

Nutrient	Average Value	Range of Values	Recommended Allowance
Energy, calories	4255	2510–6500	3000
Protein, grams	110	74–187	75
Calcium, grams	1.0	0.5–1.9	0.8
Iron, milligrams	18	11–29	12
Vitamin A, Internat'l Units	12,569	4190–30,880	5000
Thiamine, milligrams	2.4	1.5–3.9	1.5
Riboflavin, milligrams	2.5	1.5–4.1	1.9
Ascorbic acid, milligrams	112	27–280	75
Fat per energy unit, grams	210	100–384	—
Fat per person**, grams	149	65–281	—

* *See* text ("Nutritive Values of the Food Supplies") for explanation of this unit.
** Equivalent—21 meals = 1 person-unit.

the home; and 13 heads of households were retired. In 11 instances the 1953 income after income tax was under $2000; in 12 it was $2000 to $4000; and in 4 it was $4000 or over. All breakfasts, 93 per cent of the noon meals, and 94 per cent of the evening meals were from home food supplies. Guests, chiefly adults, were served 59 of the 1143 meals from home supplies, and 50 meals were eaten away from home by family members.

NUTRITIVE VALUES OF THE FOOD SUPPLIES

To evaluate food supplies nutritionally, it is necessary to have a standard for desirable nutrient-consumption. The allowances recommended by the National Research Council (1) for a man between 21 and 34 years of age, adjusted for average body size, climate and activity in the United States were taken as 1 nutrition-unit and the allowances for each person sharing the meals were related to those of the reference man.[1] In determining the number of nutrition-units in a household, both the relative allowances for each person and the number of meals from home supplies were taken into account.

In Table 1 the nutritive values[2] of the food supplies are summarized with respect to calories and seven nutrients. The recommended allowances per nutri-

[1] Allowances for the reference man and relative values for others by age and sex were supplied by the Household Economics Research Branch, Agricultural Research Service, U. S. Department of Agriculture (*see* "Application of 1953 Dietary Allowances of NRC to Population Groups in the United States" by Corinne LeBovit and Hazel K. Stiebeling, in the March 1957 issue of *J. Am. Dietet. A.*)

[2] Nutrient values for each food item were obtained from the Household Economics Research Branch, Agricultural Research Service, U. S. Department of Agriculture. Most of the items are included in Table 2, Agriculture Handbook No. 8, U. S. Department of Agriculture, June, 1950.

TABLE 2

Two levels of "adequacy" of the food supplies of individual households, in terms of nutrients

Nutrients	Percentage* of Households Having—	
	Under 110% of the NRC† Recommendation	Under 100% of the NRC† Recommendation
Calories	11	7
Protein	18	4
Calcium	44	30
Iron	15	7
Vitamin A	4	4
Thiamine	15	0
Riboflavin	37	26
Ascorbic acid	44	33

* Percentages not additive, since the same household may have been "deficient" in more than one nutrient.

† National Research Council.

tion-unit are included, to facilitate comparison. Since fat in the diet, particularly the diet of middle-aged and older persons, is of current interest, values per person[3] and per energy-unit are included, although there is no standard for comparison.

The averages in Table 1 indicate plus values for all nutrients when compared with the recommended allowances. However, the analyses were made of the food supplies as brought into the kitchen, whereas the allowances are for nutrients ingested. Although the quantities of food were adjusted according to the waste reported, accurate information concerning waste was extremely difficult to obtain, and a number of households reported none. The fact that three-fifths of the respondents reported food supplies furnishing 135 per cent or more of the calories recommended, probably indicates that more food was thrown out or fed to pets than was reported as waste.

From the range of values listed in Table 1 for each nutrient it may be inferred that the averages conceal considerable variation among households. The extent of possible inadequacy of the food supplies is shown in Table 2. Because the extent of loss of nutrients through waste was believed to be under-estimated and because no adjustments were made for losses through cooking, an arbitrary standard of 110 per cent of the recommendations for nutrients ingested was used, in addition to the more customary one of 100 per cent.

Mineral or vitamin supplements were used by 10 of the families. In the group having less than 100 per cent of a recommended value in the food supplies, the following reported using a supplement containing the deficient nutrient: calcium, 1 family; ascorbic acid, 3 families; and iron, 1 family. In general, supplements were used in families whose food supplies seemed to be adequate.

[3] The equivalent of 1 person taking 21 meals in the home.

FOODS INCLUDED IN THE WEEK'S SUPPLIES

Foods in the supplies were grouped roughly according to nutritional value. Counting 21 meals as the allottment for 1 person there were 54.43 person-units in the 27 households during the week, and the amounts per unit were:

Protein foods: Meat, fish, poultry, game (pounds)[4]	3.39
Eggs (number)	8.00
Legumes and nuts (pounds)	0.26
Cereal products: Flours, cereals, pastes (pounds)	1.35
Bakery goods (pounds)	2.18
Fat, including butter and bacon (pounds)	1.22
Milk products (except butter) milk equivalent[5] (quarts)	4.27
Sweets: Sugars, jelly, jam, candy, puddings (pounds)	1.41
Fruits and vegetables (except dry legumes and nuts):	
Citrus fruit and tomatoes (pounds)	2.36
Leafy, green, or yellow vegetables (pounds)	2.17
Potatoes (pounds)	1.72
Other vegetables and fruits (pounds)	4.89

Both sugars and fats were higher in amount than nutritionists recommend.

MONEY VALUE OF FOOD SUPPLIES

The average money value of the food supplies per week per person-unit was $7.35. This was also the median money value. The average food-supply dollar was divided in the following way:

Meat (including bacon) fish, poultry, game	$.30
Fruits and vegetables (including juice)	.20
Milk products (except butter)	.14
Other beverages (including alcoholic)	.07
Baked products	.07
Eggs	.07
Fats and oils (except bacon)	.05
Sugars and sweets	.04
Flours, meals, cereals and pastes	.03
Prepared soups, meat and cereal or vegetable mixtures, puddings, potato salad or chips	.02
Miscellaneous condiments, leavenings, pickles, gelatin	.01
	$1.00

All supplies which could not be priced by the respondent were valued at current prices in a store of the type (chain, independent, or specialty shop) in which

[4] Bacon excluded; but included .17 pound of prepared meat, fish or poultry and cereal or vegetable mixtures.

[5] Milk equivalents of dairy products (except butter) in terms of protein and minerals have been developed by the Household Economics Branch, Agricultural Research Service, U. S. Department of Agriculture. The factors used in this study for converting pounds of the products to quarts of milk were:

Evaporated milk	0.93	Ice cream	0.56
Dry skim milk	4.56	Cottage cheese (based on protein only)	2.63
Cream	0.33	American, Swiss, bleu and grated cheese	3.20

the family's food was usually bought. Purchased supplies took $6.82 of the total money value per person-unit, home produced supplies $0.19, and food received as a gift $0.33. The actual food *expense per family member* for all meals, including those to guests and meals bought away from home, was $7.49 for the week.

The money value of the home meals ranged from 16 to 56 cents per person. Under 25 cents per meal, no household had a food supply furnishing 100 per cent of all nutrient recommendations. At 25–34 cent, 4 households had supplies "adequate"[6] in all respects (even reaching the level of 110 per cent or over), and 5 did not. At 35–44 cents, 5 households had "adequate" nutrients, and 5 did not. All households at the 45–56 cents level had "adequate" supplies. The 16-cent meals were below the recommendations for every value except thiamine.

Nine of the 11 families whose yearly incomes (after income tax) were under $2000 had supplies "inadequate" in some respects, compared with 5 of the 16 families whose incomes were higher. However, other factors than income must have influenced "adequacy." In only 4 of the 27 families were the money values below those at which some families achieved 100 or even 110 per cent or more of the recommended allowances. Age is probably one factor, since in the group of 15 families with some "inadequacies," 11 had heads of the household aged 65 or over and homemakers 60 or over. Of the 12 with "adequate" supplies, only 4 were in this age group. From reading the interview reports, it was apparent that food habits (irrespective of age), frugality (irrespective of income), and ill health (temporary or continuous) were all involved. Of these, food habits seemed to be the most important factor. It is probably difficult for the aging to change these habits or, as income drops, to become adapted to less expensive forms of customary foods, or less expensive substitutes.

An overly generous supply of calories (considered nutritionally undesirable) is no guarantee that other nutrient values are high. Too often, excess calories are in the form of sweets and fat. In 6 of the 16 families with food supplies that furnished more than 135 per cent of the recommended number of calories, the food was "low" in calcium, ascorbic acid, riboflavin or some combination of these. On the other hand, in 1 of the 3 families with food supplies that provided only from 84 to 100 per cent of the calorie recommendation, the food contained all other nutrient elements in more than the recommended amounts.

SOURCES OF CALCIUM AND ASCORBIC ACID

Calcium and ascorbic acid were the nutrients most frequently at levels below the recommended allowances. Fruits and vegetables (omitting dry legumes and nuts) accounted for 93 per cent of the ascorbic acid provided by the food supplies of the 27 households. In Figure 1, food supplies have been grouped according to the level of ascorbic-acid "adequacy," showing the amounts of four classes of fruits and vegetables used per person-unit in the 27 households.

The standard employed was 110 per cent of the recommended ascorbic-acid

[6] Such terms as "adequate" and "inadequate" are put in quotation marks because we do not know how close the recommended (ingestion) allowances come to actual requirements of the persons in our study, nor what proportions of the nutrients in the supplies were lost in preparation, plate waste, or other practices.

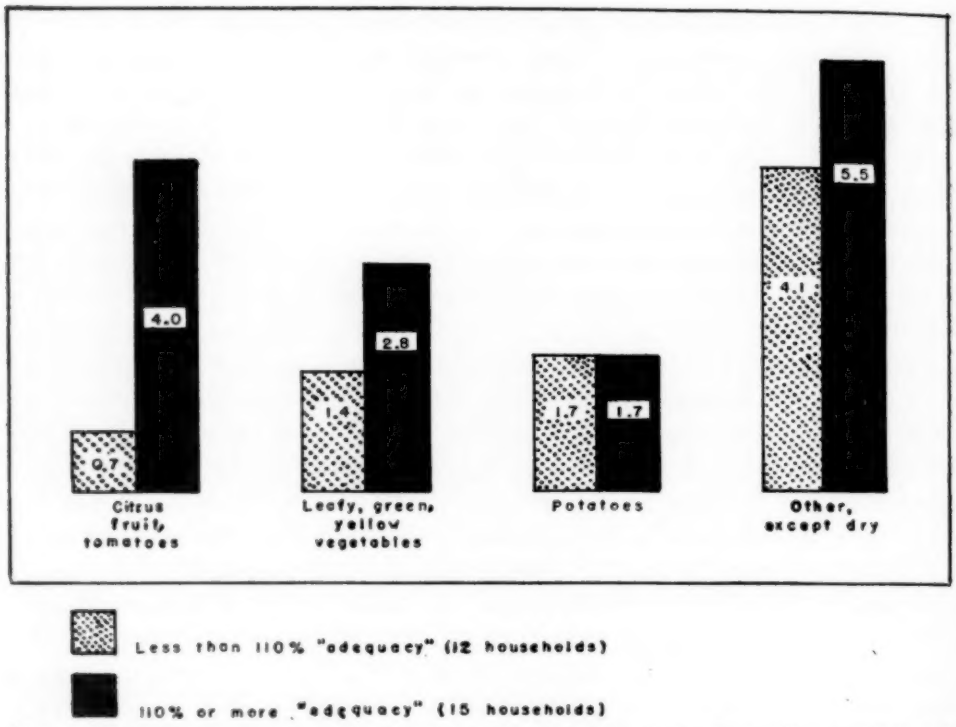

FIG. 1. Pounds per person-unit of fruits and vegetables in food supplies providing different levels of ascorbic-acid "adequacy."

ingestion, because loss from oxidation through cooking and home storage may be high (2). Important as citrus fruit and tomatoes seem to be, they are not *essential* to ascorbic-acid "adequacy." One household using none of these foods had 130 per cent of the recommended allowance.

Calcium was obtained chiefly from milk products—62 per cent. Cereal products provided 15 per cent, and vegetables and fruits (other than potatoes, dry legumes and nuts) provided 10 per cent. When food supplies were grouped according to less than 100 per cent "adequacy" and 100 per cent or higher "adequacy," very little difference was found in the use of cereal products per person-unit. Milk product equivalents (expressed as the equivalent to quarts of fresh fluid milk) were 2.2 quarts per person-unit in the low-calcium supplies and 5.1 quarts in the high-calcium supplies. The units for vegetables and fruits (excluding potatoes and dry legumes and nuts) were 6.9 pounds in the low-calcium supplies and 10.7 pounds in the high-calcium supplies.

USE OF MILK PRODUCTS

Although milk products (except butter) are especially important for supplying calcium, they are also valuable with respect to other nutrients, particularly high-quality protein and riboflavin. In the food supplies of these older families, milk products contributed 41 per cent of the riboflavin and 21 per cent of the protein. In addition, 18 per cent of the fat, 14 per cent of the calories and 10 per cent of

TABLE 3

Types of milk products used in one week

Type of Milk Product	Percentage of Households Using Product	Average Use Per Person Based on All Persons*			Range, Per Household Using the Product, (Quarts of Milk Equivalent**)
		Quantity in Pounds of the Product	Quantity in Quarts of Milk Equivalent**	Expenditure for the Product in Dollars	
Any fresh milk†	100	6.55	3.04	0.75	1.40–24.00‡
Cream	44	0.17	0.06		0.06– 0.70
Evaporated milk	33	0.31	0.29	0.05	0.85– 3.38
Ice cream	30	0.12	0.10	0.06	0.05– 2.79
Cheeses	81	0.27	0.78	0.15	0.38– 4.65
All products.....	—		4.27	1.01	1.26–26.54

* Equivalent—21 meals = 1 person-unit.

** *See* footnote 5 in text, for explanation of "milk equivalent."

† Includes fresh whole milk, skim and chocolate milks, buttermilk and half-and-half.

‡ The 24 quarts of fresh fluid milk were used chiefly by 1 person in a household of 2.71 persons, because of an abnormal health condition. The next highest amount per household was 14 quarts in a household of 2 persons.

the vitamin A and of the thiamine came from milk products. Small amounts of ascorbic acid (6 per cent) and iron (3 per cent) also came from this source.

The types of milk products used are shown in Table 3. There were no reports of the use of nonfat dry-milk-solids or condensed milk. Fifty-six per cent of the cheese was American, Swiss or bleu; the rest was cottage cheese. Expense per quart of milk equivalent varied according to the products included. Families spent from 18 to 41 cents for approximately the same protein and mineral values (those in a quart of fresh fluid milk). Relatively more households with incomes *below* $2000 spent 24 cents or more per quart of milk equivalent than did those with high incomes. At both income levels the equivalent of 3.5 quarts of milk or more per person-unit was used more frequently at the expense level of 18–23 cents (17 families) than at 24 cents or above. Van Syckle (3) has estimated that, in general, unless an adult (in Everett) has the equivalent of approximately 3.6 quarts of milk (from all sources) per week the calcium allowance will not be met. In these "older" families, weekly supplies which included less than 3.3 quarts of milk-equivalent per person (except in 2 cases) did not meet the recommendation for calcium.

FREQUENCY OF MILK DRINKING BY OLDER FAMILY MEMBERS

Milk and other foods are not necessarily used equally or according to the nutritional needs of family members. In surveys of family food supplies, information is not usually available on individual use. In the Everett survey, when menus were recorded, entries were made to show who ate the various items at a meal. Second helpings and snacks from home supplies were entered. Menus were obtained of the meals and snacks eaten away from home by each member. Although amounts were not recorded, the data indicate the food habits of the

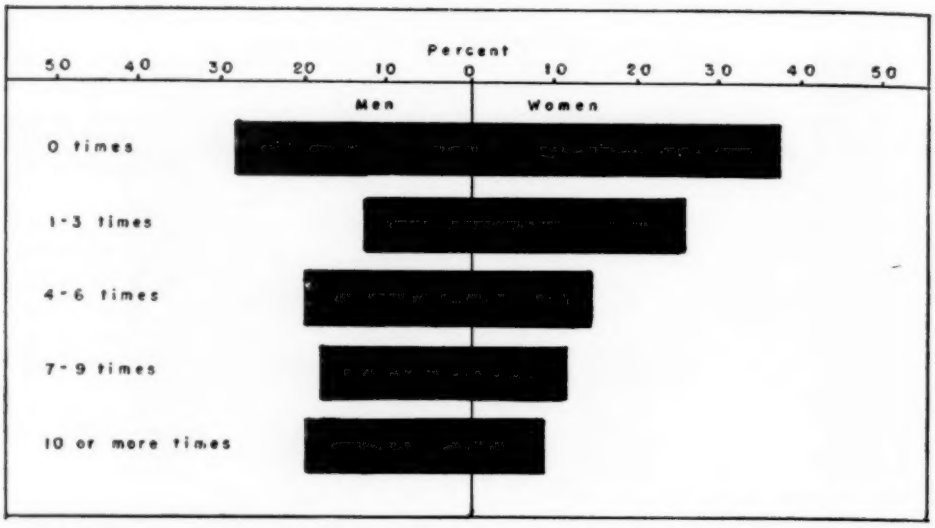

FIG. 2. Frequency of milk drinking by family members aged 50 or over. (Percentage distribution of men and of women reporting milk drunk a specified number of times during one week.)

individual family members. A total of 170 families furnished menus; they included 49 men and 48 women aged 50 or older. The number of times milk was reported drunk (except in tea or coffee) by these individuals, either at home or away, has been summarized in Figure 2.

The much less frequent drinking of milk by women than by men was striking. So was the relatively large proportion in each group who drank little or no milk (except in tea or coffee). In a study (3) of use of milk by the 226 Everett households (which included the 170 in which menus were recorded), it was estimated that 36 per cent of the members age 50 or over used either none, or less than one quart per week, including that put in coffee or tea. The frequency of milk drinking reported here is consistent with that estimate. Men and women aged 60 or over (53 members) differed much less in the frequency of milk drinking than those in their fifties (44 members). In the latter group, about three-fourths of the women compared with about one-fourth of the men reported drinking milk either not at all or less than four times during the week.

SUMMARY

Food supplies of 27 "older" families studied had an average nutrient value well above that recommended by the National Research Council for nutrients ingested. However, 14 of the households had supplies deficient in one or more nutrients. If amounts had been adjusted for losses through cooking and more accurately adjusted for waste, the number showing deficiencies would have been higher. Ascorbic acid, calcium and riboflavin were the nutrients most frequently found in less than the recommended amounts.

The money value of "adequate" supplies ranged from 25 to 56 cents per person-unit per meal; and that of "inadequate" supplies, from 16 to 44 cents

per meal. The proportion of families having adequate supplies increased as income increased. Although low income may have been a factor in determining the adequacy of food supplies, food habits were probably much more important.

Loss of ascorbic acid in the preparation of food may be high. Supplies furnishing 110 per cent of the recommendation for ascorbic acid included, on the average, four times as much citrus fruit and tomatoes, twice as much leafy, green and yellow vegetables, the same amount of potatoes, and a third more other fruits and vegetables than did the supplies furnishing less than 110 per cent of the ascorbic acid standard. Supplies furnishing 100 per cent or more of the recommendation for calcium included, on the average, more than twice the equivalent of fresh milk and 55 per cent more vegetables and fruits (excluding potatoes, dry legumes and nuts) than did supplies furnishing less than 100 per cent of the calcium standard. Low riboflavin values were associated with low calcium or low ascorbic-acid content of the supplies.

Different combinations of fresh and evaporated milk, cream, ice cream, and cheese (in values converted to milk-equivalents) cost the families from 18 to 41 cents per quart. Costs *under* 24 cents were associated more frequently with yearly incomes *above* $2000 than under. At either income level, the use of as much as 3.5 quarts of milk-equivalent per person-unit was more frequent when expense per quart was 18–23 cents than when it was higher.

Information on the frequency of milk drinking by all members aged 50 or over in 170 families showed a relatively high proportion of each sex drinking little or none (excluding use in tea or coffee). On the whole, women drank milk much less frequently than men. The sex difference in milk drinking was much greater in the group aged 50–59 than in the older group.

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HOST-TUMOR ANTAGONISM. VI. THE INFLUENCE OF THE THYROID HORMONE IN MALIGNANT DISEASE

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INTRODUCTION

In this essay it is planned to develop the thesis that many tumors besides being estrogen-dependent or androgen-dependent, may also be thyroid-dependent. The effect of the thyroid on tumors may be expressed directly, or through inhibition of the pituitary gland by thyroid hormone. There is also interesting geographic evidence linking the presence of thyroid dysfunction with the incidence of malignant disease.

Practically every chemical reaction occurring in the body is an enzymatic one, and presumably under the control of thyroid hormone.

The question arises, how does the thyroid hormone act as an anti-carcinogen? Thyroid hormone depresses the activity of the pituitary gland, perhaps in a different way from the estrogens. It has various other salutary actions. Its effect on growth, maturation and differentiation are probably important, being of a metamorphosing nature, in contrast to the growth action of the pituitary growth hormone. It inhibits the production of vaginal cornification by estrogen.

I. THE EFFECT OF THE PITUITARY GLAND ON TUMORIGENESIS

It has long been known that hypophysectomy retards the development of tumors in rats. Ball and Samuels (1) noted that the growth rate of a transplantable mammary carcinoma was markedly reduced in a group of hypophysectomized albino rats. When the hypophysectomy was performed after development of the tumor, there was an immediate retardation of the neoplasm. However, in this series, growth of the tumors did not cease completely.

Moon, Simpson and Evans (2) noted that in 12 of 15 rats implanted with methylcholanthrene pellets there was a palpable increase of connective tissue at the implantation site, and that in 8 of these rats rapidly growing tumors developed. These lesions did not occur in any of the normal controls. In a group of 15 hypophysectomized rats treated with methylcholanthrene, in only 1 did a sarcoma develop at the site of implantation. There was little or no connective tissue reaction to methylcholanthrene in the hypophysectomized animals.

Moon and associates (3) noted that the long-term administration of pituitary growth hormone to 15 normal rats resulted in atypical hyperplasia of small follicles in 5 rats and solid ovarian tumors in 2 rats. There were no similar changes in the control rats. This atypical hyperplasia of small follicles was considered to be an early stage in the development of granulosa-cell and interstitial-cell tumors of the ovary. Fibroadenomata of the breasts occurred more frequently, were larger and were often multiple in rats injected with growth hormone.

* F.A.C.A. Parts I–V have been published in the July, August, November (1956), April and May (1957) issues of this journal.

Moon and co-workers (4) also found that injecting adult female rats with pure growth hormone for long periods resulted in general body growth amounting to gigantism. Lymphosarcoma of the lung occurred in 6 of 15 rats given injections of pituitary growth hormone, but no similar tumors occurred in control rats. In all the rats treated with growth hormone, there was hyperplasia of the peribronchial lymphoid tissue, and lymphosarcomatous transformation was observed in some of these areas.

Biskind and Biskind (5) induced ovarian neoplasms by transplanting ovarian tissue into the spleens of castrated rats. These authors noted no growth of the intrasplenic transplants of ovarian tissue in hypophysectomized rats. One theory is that this neoplastic transformation was dependent on the inactivation of estrogen by the liver of the castrated rats; this inactivation resulted in abnormal stimulation of the intrasplenic ovarian tissue by excess gonadotropins.

In a very recent study, it was noted again by Moon, Li and Simpson (6) that carcinogenesis is suppressed by hypophysectomy. When 9,10-dimethyl-1,2-dibenzathracene was administered to intact animals, malignant tumors almost invariably formed at the site of injection. In hypophysectomized rats, the latent period between injection and appearance of nodules was longer, the incidence of tumor production was lower, and the growth of neoplasms was slower than in rats with intact pituitary glands.

However, the refractory state of the hypophysectomized animal to carcinogenesis was relative and not absolute. Other factors were species, age, carcinogenic stimuli, nutrition, and length of the period of observation.

The neoplastic response could be reinstated in hypophysectomized rats by administration of crude pituitary extract and by purified growth hormone. When either agent was used, the response approximated that of rats with intact pituitaries. The administration of adrenocorticotropic hormone to hypophysectomized rats did not restore the carcinogenic response to 9,10-dimethyl-1,2-dibenzanthracene.

Moon, Li and Simpson believe that the carcinogenic response parallels body growth and is modified by pituitary hormones. Rats that were hypophysectomized and did not receive replacement therapy lost, and did not regain, weight. When pituitary extract was injected, the animals grew rapidly and eventually exceeded the size of rats with intact pituitary glands. Injection of adrenocorticotropic hormone alone did not restore body growth. They felt that factors which promote or inhibit body growth probably affect carcinogenesis in a similar manner. Restriction of caloric intake sufficient to depress body growth also depresses the incidence and delays the appearance of tumors.

Inasmuch as both pituitary hormones and nutrition modify the carcinogenic response, the interrelationship of these factors is pertinent. Pituitary secretions modify nutritional requirements and utilization of dietary constituents.

The growth hormone promotes nitrogen retention and protein synthesis. The inhibitory effect of adrenocorticotropic hormone on body growth is due to interference with protein synthesis. Therefore, the difference in carcinogenic responses after injection of these hormones may be attributable to the different influences

of the substances on protein metabolism. It seems hardly likely that this is the only action of pituitary hormone that promotes tumorigenesis.

In the treatment of widespread breast cancer in humans by hypophysectomy, it does not appear that removal of the pituitary acts in this way. Luft and Olivecrona (7) performed hypophysectomy on 9 patients with far advanced carcinoma of the breast who had a recurrence after mastectomy, and widespread metastases. Although the follow-up period following hypophysectomy was short, the authors stated that this operation was well tolerated, but that unless it were complete, the effect was only temporary and of short duration. They describe a 49-year-old patient who experienced remarkable regression of the carcinoma following hypophysectomy. However, the improvement was of a temporary nature. Luft and Olivecrona performed incomplete hypophysectomy on 1 patient with carcinoma of the prostate gland. Difficulty of urination disappeared, and there was relief of pain until death, which occurred four months after the operation.

Recently, Luft (8) made an additional report on the treatment of 75 cases of advanced cancer of the breast or the prostate, up to January 1, 1956. In these patients, the pituitary gland was removed and the area was treated with radiation to assure that all pituitary activity was destroyed. The operation was performed in 52 women who had advanced and spreading cancer of the breast. In 22, there was some improvement. However, only 1 case remained improved after two years. The average duration of benefit was limited to a period of seventeen months. Similar surgery in cases of advanced prostatic cancer achieved an improvement that lasted only two to three months in 2 of 5 patients who benefited.

Peters (9), in a recent study of hormone therapy in metastatic carcinoma of the breast, noted that there was a poor response to testosterone therapy when castration-irradiation was administered concurrently with the course of testosterone. It was felt, therefore, that testosterone therapy has a much different biologic effect and that on this basis alone, these two treatments should not be carried on simultaneously. Testosterone may act by inhibiting pituitary activity (acting as medical hypophysectomy) rather than antagonizing the hormone-dependence of the tumor. Peters noted that there was often a dramatic response to estrogen in women of the menopausal age group after testosterone had failed, and advised a trial with both hormones. This response could be due to the superior effect of estrogen in antagonizing the pituitary hormone in some patients.

II. THE MANNER IN WHICH THYROID HORMONE MAY ANTAGONIZE PITUITARY SECRETION

It has been generally accepted that secretion of gonadotropic substances may be inhibited by the sex hormones. Chen and You (10) suggest the possibility that the inhibitory action of estrogen on the pituitary is caused by stimulation of the thyroid. This assumption is strengthened by the finding that a considerable degree of ovarian inhibition has been achieved by the administration of large doses of desiccated thyroid to intact rabbits.

Laqueur and Emge (11) hold the view that estrogenic hormones depress the

gonadotropic apparatus more effectively in the presence of a hyperplastic thyroid. Thus the thyroid hormone may potentiate the action of estrogen. These authors observed accidentally that large doses of estrone induced hyperplasia of the rat thyroid. Withdrawal of the ovarian hormones by castration produced morphologic evidence of decreased thyroid activity.

III. THE EFFECT OF THYROID HORMONE IN REDUCING TUMORIGENESIS IN EXPERIMENTAL ANIMALS

Bather and Franks (12) observed that the incidence of tumors at the site of injection of chemical carcinogens was reduced by a single injection of thyroxine or other metamorphosing hormones given with the carcinogen. Additional studies showed that the rate of disappearance of carcinogen from mice was significantly increased by the thyroxine treatment. After four weeks of injections of 1,2,5,6-dibenzanthracine into mice treated or untreated with thyroxine, the amount of carcinogen remaining in the carcasses was significantly lowered in the thyroxine-treated animals.

Thyroxine feeding lowers the sarcomagenic action of dibenzanthracine in mice, whereas thiouracil feeding markedly increases the incidence of sarcoma. Since thyroxine has been found to have little or no effect on the growth of already established tumors, *e.g.*, transplanted sarcomas, Bather and Franks feel that it may play an important part in the normal cell's defense against chemical sarcomagenesis by increasing the metabolic destruction of the carcinogen.

Hepbisul (heptyl aldehyde-sodium bisulfate) and natural thyroxine were administered subcutaneously by Herbut and associates (13) to 108 rats bearing Walker rat carcinoma 256. In 36 per cent there was a salutary effect, as shown by regression of the tumors or a favorable histologic response. However, when synthetic thyroxine was substituted in the combination, only 4 per cent of the rats had a favorable response.

Granulosa-cell tumors, luteomas, tubular adenomas, and mixed-cell tumors have developed in intrasplenic ovarian grafts in castrated mice of the strains studied by Miller and Gardner (14). It was postulated that hypersecretion of gonadotropins might be the tumorigenic agent.

The effects of hypothyroidism and of hyperthyroidism were also observed by these authors, because these may alter the type or amount of gonadotropins that are secreted or they may alter the end-organ response. In 2 of 20 hyperthyroid mice, in 10 of 21 hypothyroid mice, and in 16 of 21 euthyroid animals, ovarian tumors developed. Adrenocortical hyperplasia was marked in the euthyroid mice and absent or minimal in the hyperthyroid animals. The authors concluded that ovarian tumorigenesis paralleled the development of adrenocortical hyperplasia. It is especially interesting for our thesis that five times as many ovarian tumors developed in hypothyroid mice as in hyperthyroid mice.

IV. THE GEOGRAPHIC INCIDENCE OF THYROID DYSFUNCTION AS COMPARED WITH THE GEOGRAPHIC INCIDENCE OF CANCER

After much study, it would appear that the variable incidence of malignant disease throughout the world is conditioned by local factors and is not due to

faulty methods of diagnosis or inadequate methods of death registration. Differences of cancer incidence between localities is probably not due to racial factors, but to environmental factors (15). Nordling (16) noted the great difference in the frequency of cancer between white persons in northeastern and in southern United States, as well as between Negroes in these two regions. The incidence of cancer in the Negroes of each area tended to approach that of the white persons in the same area.

Spencer (15) analyzed the geographic incidence of goiter and compared it with the incidence of cancer. He found that in many instances the two coincided. For example, the incidence of cancer in Belgium is lower than in Holland, and the incidence of goiter is likewise lower.

The World Health Organization lists Holland as having probably the highest cancer incidence in the world, and it is noted by Spencer that Holland has a great goiter problem that has been known for centuries. Spencer drew conclusions, based on the survey of Stocks (17), that in certain goitrous counties in both Sweden and Norway there is a high death rate from cancer. Spencer pointed out that although Iceland consists of people of Norwegian stock with some Danish admixture, and although the incidence of cancer in Norway and Denmark in very high, the incidences of both goiter and cancer are distinctly lower in Iceland. Goiter is rarer in Portugal than in Spain, and so is cancer.

Stocks (17) reported a close statistical relationship in the various cantons of Switzerland between the incidence of goiter and the incidence of cancer of the stomach and esophagus. In the United States, Stocks found a good correlation in the various states between the incidence of goiter and the incidence of esophageal and gastric cancer. In Japan, where almost no goiter exists due to the large amount of iodine ingested with fish and seaweed, the figure for cancer incidence is one of the lowest in the entire world.

In another study, Legon (18) observed that the areas of heaviest total cancer mortality in England and Wales are the areas of soils richest in organic matter, and that these heavy mortalities may be related to differences in the micronutrient content of crops grown in peat soils. Legon found that there was a high total cancer mortality in populations living in the vicinity of soils with high organic content. This suggested that a carcinogen may exist in food plants grown in soils of high organic content or that a protective substance was lacking in such plants. He suggested that it may be a copper deficiency, since this element is sometimes lacking in crops grown on peat. In any event, this is another contribution to the theory that carcinoma is a regional event, rather than a racial occurrence.

V. CLINICAL INVESTIGATIONS

According to Loeser (19), adjuvant treatment of recurrent cancer of the breast with male hormone is only partially successful, because in the long run, it will kill the patient by more or less completely blocking the anterior pituitary gland. It may shrink the pituitary gland to about a third its normal size, as observed at necropsy, and may eventually rob the body of adrenotropic and thyrotropic hormones.

Loeser employed thyroid hormone for prophylactic treatment after operation for mammary and genital cancer. He reported figures to prove that hyperthyroid patients rarely suffer from cancer. After partial thyroidectomy (when about seven-eighths of the gland was removed) a greater number of genital and mammary cancers develop in women between 40 and 60 years of age than in the average population of the same age and sex. Cancer develops in only about 0.5 per cent of hyperthyroid patients, whereas it occurs in about 7 per cent of thyroidectomized patients. As an example, he cited 14 gynecologic patients who had previously undergone a thyroidectomy (13 because of nodular goiter and 1 because of toxic goiter). In 6, benign tumors of the uterus or ovaries developed, and in 8, a carcinoma of the breast was found two to five years after thyroidectomy. Loeser cited 2 special examples. One patient had a partial thyroidectomy for nodular goiter, and an early breast cancer was discovered; two days later a radical mastectomy was performed, and the patient died from rapidly developing metastases. The other patient had a radical mastectomy for early carcinoma of the breast, and three years later a nodular goiter was removed. The patient died from metastases six months after the thyroidectomy.

Loeser considers a low level of lipids in the blood to be a prophylactic factor against recurrence of cancer, and that the lipid level can be decreased by thyroid therapy. Patients with hyperthyroidism and with allergic conditions have an excess of intracellular histamine in the skin, and Loeser believes that in these two types of disease there is a lower incidence of cancer than in the normal population. There is some difference of opinion on the point, however. Histamine in the skin increases variably after thyroid administration, and may be as high as 133 per cent. He concludes from this phase of his research, that there is a quantitative relationship between the amount of thyroid hormone in the body and the intracellular deposition of histamine. The more thyroid hormone, the more histamine and the lower the lipid level of the blood.

Loeser believes that it is logical to treat women permanently with desiccated thyroid after radical mastectomy and radiation therapy for cancer of the breast and after operations for genital cancer. He cites 18 patients treated by this new technique since 1948. Four have been under observation for more than five years; 2 had carcinoma of the breast with axillary metastases, 1 had bilateral ovarian cancer with peritoneal spread, and 1 had endometrial cancer. These 4 patients are all alive and well, and 14 additional patients were observed for more than four years after mastectomy. There was only 1 recurrence—metastasis to the brain. Loeser regards a plasma cholesterol level of 150 to 175 mg. per 100 cc. as desirable, and sufficient thyroid hormone should be given to approximate this level.

Crile (20) believes that some well differentiated cancers of the thyroid can be controlled by thyroid therapy. A dosage of 3 to 4 grains daily is required, which presumably furnishes so much thyroid hormone that it depresses the thyroid-stimulating hormone of the pituitary. The thyroid gland, deprived of pituitary stimulation, atrophies.

Crile recounts the history of a patient with oxyphilic adenocarcinoma of the thyroid (Hürthle-cell cancer) who presented hyperthyroidism with chest me-

tastases. These metastases had remained quiescent for at least two years. When Crile used radioactive iodine for treatment, the hyperthyroidism regressed, but the metastatic tumors enlarged rapidly and the patient soon died.

Crile followed 5 patients with pulmonary metastases from papillary thyroid carcinoma, treated with desiccated thyroid for from one to five years. In each case the carcinoma stopped growing, and there was clearing of the chest roentgenograph. Similar results were reported by Balme (21) in England.

Crile (22) believes that papillary carcinoma of the thyroid may be spread by needle biopsy and by any operation that cuts into the tumor. On the basis of experience with 107 cases of papillary carcinoma of the thyroid, he found that the incidence of metastasis from the neoplasm was ten times as high when a biopsy specimen had been taken as when the tumor had been completely removed and not cut into. In a series of 84 consecutive cases in which no biopsy, or incomplete operation had been performed before the primary tumor was removed, no distant metastases had occurred during a period from one to eighteen years after operation and none of the living patients had a recurrence of cancer.

Crile feels that there is a fairly high host resistance to recurrence of papillary carcinoma of the thyroid. However, that resistance may be reduced when myxedema is induced by treatment with radioactive iodine or total thyroidectomy. Following this therapy, he observed rapid growth of metastases. He believes that the rapid growth of the tumor may be caused by the thyroid-stimulating hormone of the pituitary, which is produced in excess when there is a deficiency of circulating thyroid hormone. Conversely, when the thyroid-stimulating hormone is inhibited by giving large doses of thyroid (3 grains or more daily), metastases regress or disappear. Crile observed this effect in 7 patients.

Based on somewhat inadequate evidence, the Levys (23) contend that the hypometabolic state as found in hypothyroidism is inimical to the presence of cancer. However, the quotations presented from the literature suggest exactly the opposite in several instances. For example, it is stated that investigations have shown the anticarcinogenic effect of the antithyroid drugs, but the reference quoted concerns the experimental production of thyroid tumors in the rat exposed to prolonged treatment with thiouracil (24). The Levys correctly state that prolonged administration of pituitary growth hormone results in tumorigenesis, and assume without adequate evidence that the hypermetabolic state favors this special situation. The reverse is probably true. In the case history cited to prove that the hypometabolic state is antagonistic to cancer, the more likely possibility is that the intake of desiccated thyroid may have been one factor explaining the patient's exceptionally long survival with lymphoblastoma.

VI. DISCUSSION AND RECAPITULATION

It has been known for years that thyroid activity decreases with advancing age. Basal oxygen consumption of the total body diminishes gradually with increasing age (25). This reduction is maintained even when the determinations are corrected for differences in body size, based on estimates of surface area. In all probability, the basal metabolism per unit of surface area of females re-

mains below that of males even at advanced age. Shock (25) believes, however, that this means reduction or loss of activity of body tissues and cells having relatively high rates of oxygen consumption, rather than reduction in over-all metabolic activity. However, we do not know which possibility represents the actual situation. It is natural that attempts should be made to link the lowered metabolism of aging people to the increased incidence of cancer in this period of life.

There are several ways in which the thyroid hormone may be effective in influencing the growing cancer.

1. Thyroid hormone encourages physiologic tissue respiration rather than the anaerobic type which is stated to be a characteristic of carcinoma.

2. Thyroid hormone is important in stimulating cellular differentiation in the normal embryo. One of the characteristics of the carcinomatous cell is the de-differentiation that it has undergone; thyroid hormone may reverse this process.

3. Thyroid hormone, by raising the oxidative rate, may induce greater catabolism or an increased rate of excretion of a carcinogen.

4. Thyroid hormone may inhibit pituitary activity, by virtue of the reciprocal relationship between the two glands.

5. Thyroid hormone seems to be antagonistic to the depolymerization of connective tissue brought about by pituitary thyrotropic hormone. Connective tissue is believed to be an important link in the resistance of the host to cancer. Thyroid hormone can induce polymerization of the muco-polysaccharides of connective tissue (15).

Animal experiments have indicated the reciprocal effect of thyroid activity on malignant growth. Miller and Gardner (14) attempted to graft granulosa-cell tumors, luteomas and tubular adenomas into the spleens of mice, under varying conditions. When the mice were receiving a normal diet, 76 per cent of the grafts were successful, whereas when 0.2 per cent thyroxine was added to the diet, only 10 per cent of the grafts were successful.

Bather and Franks (12) noted that the rate of disappearance of carcinogen injected into mice was greater in thyroxine-treated animals. Thus the incidence of tumors at the site of injection of 1,2,5,6-dibenzanthracine (DBA) was reduced by a single injection of thyroxine. With varying dosage of DBA, simultaneous administration of thyroxine lowered the tumor response significantly at each level. Thiouracil feeding increased the incidence of DBA-induced tumors. It was shown by Herbut, Kraemer and Jacksen (13) that natural thyroxine was more effective than synthetic thyroxine as an antagonist to the growth of Walker rat carcinoma.

Rusch and Bauman (26) found that the addition of wheat, yeast or casein delayed the onset of liver tumors in rats fed butter yellow (p-dimethyl-aminobenzene). These proteins all contain a fairly high content of tyrosine, which is a precursor of thyroxine.

Purves, Griesbach and Kennedy (27) showed that a thyroid tumor which had occurred in a rat after prolonged thiouracil administration, could be transplanted into another rat, if this animal were made thyroid-deficient. Following this

transplantation, the tumor could thereafter be transplanted into euthyroid animals. At this stage, the tumor had apparently become autonomous.

Fouldes (28) noted that some spontaneous mammary tumors in mice would grow rapidly during pregnancy and then regress post partum. This effect was apparently not due to progesterone or estrogen. That thyroid deficiency may occur during pregnancy is well known, and Spencer believed that thyroid deficiency in pregnancy could account for the findings.

Recent work by Moon and his co-workers (2, 3, 4) has shown rather conclusively that extract of anterior pituitary hormone causes the development of tumors of various types in laboratory animals and, conversely, that extirpation of the pituitary retards tumor growth or inhibits the carcinogenic effect of methylcholanthrene. Similar findings were demonstrated by others years before. Luft and Olivecrona (7) by means of hypophysectomy have altered slightly the downhill course of women with advanced mammary carcinoma unresponsive to mastectomy, radiation or hormonal therapy.

It is possible that favorable results of therapy with estrogens or androgens in cases of advanced mammary carcinoma are accomplished by means of a temporary, partial medical hypophysectomy. Doubtless, other actions of these hormones may also play a part, but perhaps one of the important functions of the sex hormones is to reduce pituitary activity. The thyroid hormone also has a reciprocal action with the pituitary hormone. Pituitary gonadotropin stimulates the ovary to produce estrogen, and when the blood level of estrogen rises sufficiently, the secretion of the gonadotropic hormone is depressed. In like manner, a low level of thyroxine in the blood acts as a stimulus to the secretion of pituitary thyrotropic hormone, and a high level of thyroxine acts as a brake on the secretion of thyrotropin. Thus both thyroxine and the sex hormones act to suppress the activity of the pituitary gland.

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Abstracts of Current Literature

A SCREENING TEST FOR ACHLORHYDRIA WITHOUT INTUBATION. A SURVEY OF 90 MALES OVER 40 YEARS OF AGE.

Bertone, A. E., and Sinclaire, H. A. *Indust. Med. & Surg.* **25:** 563 (Dec.) 1956.

The Diagnex test is an easy and inexpensive method for determining achlorhydria in ambulant patients. It employs a cation exchange indicator compound, carbacrylic quinine resin. A dose of 2 grams of the substance is administered orally one hour after gastric stimulation with 250 mg. of caffeine sodium benzoate. The control urine is collected one hour after ingestion of the latter, and the sample specimen two hours after taking the resin. The urines are examined by extracting the quinine present by the ether sulfuric-acid technic of Kelsey and Geiling. The degree of fluorescence observed in the control urine is a reliable means of detecting the presence of interfering materials; when they are present, the test must be repeated after a week. The various drugs that interfere with the results of the quinine assay are listed. In interpreting the urinary findings, 25 to 30 μg. or more of quinine indicates the presence of free hydrochloric acid, 15 to 25 μg. indicates possible hypoacidity, and 15 μg. or less indicates the absence of free hydrochloric acid and a diagnosis of achlorhydria. The test is invalidated by pyloric or intestinal obstruction; persistent vomiting interferes with the absorption or retention of quinine; rapid emptying of the stomach due to partial gastrectomy may result in low values; and advanced renal failure may interfere with quinine extraction and result in low values. Side-effects are negligible and the only contraindication is known sensitivity to quinine. The Diagnex test was used in screening for achlorhydria in 90 patients over 40 years of age. Eight, or 7.7 per cent, had achlorhydria. None had a positive finding upon roentgenographic examination of the gastro-intestinal tract nor evidence of anemia. One of the patients was given a histamine test meal and a fractional gastric analysis performed. By this method also he was not found to have achlorhydria. The test is mandatory in cases of pernicious anemia. Its applications in other diseases are reviewed.

PSYCHOLOGICAL LIMITATIONS THAT OCCUR WITH AGE.

Birren, J. E. *Pub. Health Rep.* **71:** 1173 (Dec.) 1956.

General age trend explains some of the variation in data for many psychological and biological processes. There is also a large range of individual differences. It depends upon aims, whether the general age trend or the individual differences in aging should be emphasized. Probably the most significant result of research on age changes in the nervous system in the past ten years is the implication that there is a general slowing of all voluntary responses. Data from the literature are presented which indicate that the age change in response latency may be regarded as a general property of the central nervous system. Experiments on speed in timing in human behavior are cited. The older person is most comfortable in a situation wherein he can pace his responses and is least comfortable in one in which he must respond quickly to demanding sequential stimuli. The delayed responses in the elderly appear to have their greatest consequence for complex or serial activities. Perceptual difficulty can contribute to the slow response of elderly subjects. These facts offer suggestions for further research into the bases for the changes and for so arranging the environment of the elderly as to reduce problems of living due to the psychological limitations of aging.

DIAGNOSIS OF UTERINE-TUBE CARCINOMA BY VAGINAL CYTOLOGY.

Brewer, J. I., and Guderian, A. M. *Obst. & Gynec.* **8:** 664 (Dec.) 1956.

Positive and atypical findings in vaginal cytosmears from 3 patients with tubal carcinoma are reported. In 2 instances, the malignant growth was primary in the tube, and in 1 it was

secondary to an undiagnosed carcinoma of the pancreas. All 3 patients had a history of abnormal bleeding—2 in the postmenopausal period and 1 in the climacteric. Curettage of the uterus and biopsies of the cervix failed to demonstrate carcinoma of the uterus in 2 of the 3 patients. Curettage in 1 patient was impossible, due to the presence of a firm cervical stricture. Persistently positive cytosmear findings in cases in which diagnostic curettage and cervical biopsies yield negative results suggest either that the latter procedures have failed to locate the uterine malignancy or that the neoplasm is located beyond the uterus in the tube, ovary, or peritoneum. Complete medical investigation and, in rare instances, abdominal exploration are indicated in those patients in whom the cytosmear findings are persistently positive or atypical but in whom curettage and cervical biopsies have failed to demonstrate a uterine carcinoma. The early diagnosis of ovarian and tubal carcinoma, both primary and metastatic, is notoriously difficult due to the absence of symptomatology and the often rather insignificant bimanual findings. The routine employment of the vaginal cytosmear as a diagnostic screening procedure for malignancy of the female genitalia is a significant advance in the diagnosis of these lesions. (From authors' conclusions).

IL CANCRO DELLA LINGUA E LE SUE METASTASI. RENDICONTO CLINICO-STATISTICO DI 772 CASI (CANCER OF THE TONGUE AND ITS METASTASES. CLINICAL-STATISTICAL REPORT OF 772 CASES).

Bucalossi, P., and DiPietro, S. *Tumori* **42:** 244, 1956; through Ciba Literature Review **1:** 289 (Oct.) 1956.

During the past few decades, the Istituto Nazionale Tumori in Milan has treated 772 patients with cancer of the tongue—a figure corresponding to 3.5 per cent of all tumor patients admitted over the same period. Eighty-four per cent of these patients were men. Apart from smoking, other factors likely to cause cancer of the tongue are traumatic irritation set up by the teeth or dentures, leukoplakia, papillomas, and syphilis. In 85 per cent of cases, the tumor was situated wholly or mainly on the movable portion of the tongue. The symptoms of cancer of the tongue are slow to develop. Even in the most advanced stages, it may cause the patient little discomfort. Treatment consists of local application of radium needles or surgical intervention. These forms of therapy are often combined. A good response may be expected in 77 per cent of cases. The chances of recovery have improved appreciably with the course of time. Whereas at one time only 21.4 per cent of the patients were still alive five years after treatment, the average over the past fifteen years has been 38.6 per cent. Glandular metastases are present in 60 per cent of cases, and in the early stages are often difficult to recognize. For this reason, the lymph glands of the neck should always be removed when operating for cancer of the tongue. Using this radical procedure, the recovery rate was 42 per cent among 212 patients. Among patients whose lymph glands were not removed, the rate was only 35.3 per cent, although on the whole these patients had not reached such an advanced stage.

PHYSIOLOGICAL LIMITATIONS AND AGE.

Falzone, J. A., and Shock, N. W. *Pub. Health Rep.* **71:** 1185 (Dec.) 1956.

Experimental studies on physiological changes with aging are reviewed. The first of these deal with changes in internal environment and include the findings in older people of 1) lack of change in body temperature and in the levels of various substances in the blood, 2) maintenance of the acid-base equilibrium within normal limits, 3) slight fall in pH of the blood with increasing changes in CO_2 tension and bicarbonate level, 4) no significant change in arterial fasting blood sugar but evidence for a slightly higher fasting level in venous blood, and 5) well maintained hematological values. Functional measures show that 1) the oxygen consumption per individual decreases with age, 2) the resting cardiac output and cardiac index decline, 3) pulmonary function changes markedly with a decline in total lung capacity that is paralleled by a decline in surface area, 4) the compartments of total

lung capacity change with an increase in residual volume at the expense of vital capacity 5) maximum breathing capacity falls, 6) renal plasma flow, as measured by Diodrast clearance, decreases, 7) the glomerular filtration rate decreases, 8) the filtration fraction increases, implying a relative increase of efferent to afferent arteriolar constriction, 9) the decrease in renal blood flow with age exceeds that in cardiac output so that it would appear that total renal resistance has increased more than total peripheral resistance, 10) a large proportion of the total as well as the relative efferent vasoconstriction present in an old kidney is reversible, and 11) tubular function as estimated by maximum rates of Diodrast excretion and glucose reabsorption decreases with age, the magnitude of the decrement being similar to that of the glomerular filtration rate. The possible effects of these changes upon longevity are discussed. It is concluded that the primary characteristic of the older person is a reduction in reserve capacities which makes him more vulnerable to stress even of daily living than a younger person. These changes take place gradually over the adult life span and may be attributed in part to loss of functioning tissue, the causes for which have not been identified. An outstanding characteristic of age is the striking difference in vulnerability among persons. Factors which account for these differences have not been identified nor has the relative importance of loss of functioning tissue and alterations in cellular metabolism in producing age changes in physiological function been determined. To answer questions like these, extensive biochemical, physiological, and histological studies on species other than man will be required.

DIAGNOSIS OF OVARIAN CARCINOMA BY VAGINAL CYTOLOGY.

Figge, D., and DeAlvarez, R. R. *Obst. & Gynec.* **8:** 655 (Dec.) 1956.

Carcinoma of the ovary, usually diagnosed in late stages, illustrates the importance of early diagnosis as a prerequisite to satisfactory therapy and prognosis. The results of a survey in retrospect of 10 patients with ovarian carcinoma from whom vaginal smears were obtained prior to diagnosis are encouraging. Seven smears indicated a diagnosis of malignancy and 2 were highly suspicious. Small atypical glandular cells were uniformly exhibited in the vaginal smear of each patient with ovarian carcinoma. This association has been noted by other observers and suggested that the positive smear is not necessarily an uncommon finding and that vaginal smears carefully screened by competent cytologists might provide a means of early diagnosis of such lesions. The value of the smear as a screening aid has not been established but it can be of value in a direct approach. Vaginal smears which indicate malignancy justify an investigative diagnosis of genital or abdominal carcinoma. When malignancy of the vagina, cervix or uterus is absent, another possibility is ovarian carcinoma. False positive findings with vaginal smears are uncommon.

REHABILITATION OF THE ELDERLY AMPUTEE.

Grynbaum, B. B., and Gordon, E. E. *J. Chron. Dis.* **4:** 292 (Sept.) 1956.

Vascular impairment, which occurs with increasing frequency in elderly persons, usually implicates the legs and rarely the arms. The causes in order of frequency are arteriosclerosis, embolism, Buerger's disease causing gangrene, frostbite, malignancies of bone and soft tissue, and trauma. Every elderly amputee should have a complete physical examination as part of the evaluation to decide the feasibility of a prosthesis, inasmuch as the general state of health is often the determining factor. Physiologic rather than chronologic age is important. Heart disease is not a contraindication. Some of the difficulties arising at the anatomic site are adherent scars, neuromata, exostosis, infection, poor anatomic conditions due to inadequate shrinkage, breakdown of the skin from local allergies, contractures of proximal joints, and reduction in strength from disuse. The absolute contraindications to the prescription of a prosthesis are severe cardiovascular disease, inadequate motor coordination, and senile mental changes. Severe loss of vision or complete blindness is not a contraindication but the training of blind persons is extremely difficult. Psychologic factors require the most careful consideration. Complaints arising from unfavorable personality characteristics

may be mistaken for pain due to physical causes. Without psychiatric assistance in these cases, the best prosthetic skill is of no avail. Following amputation, depression and emotional manifestations of psychic trauma should not interfere with planning the prosthetic procedure. Resuming the biped position may be an important component of psychotherapy. Preservation of the knee joint facilitates rehabilitation. The deciding factor in prescribing a suction socket is the strength of the upper extremities. It is contraindicated by muscle weakness and loss of muscle mass of the affected limb. The economic problems of the elderly amputee deserve the same attention as his medical problems. Rather than have him leave his home to become a charge of the community, an attempt should be made to meet the cost of a prosthesis through community facilities. Prosthetic training should be encouraged against the day of possible loss of both limbs, because most vascular diseases of the lower limbs are symmetrical. Without previous experience in the use of one artificial limb, a double amputee has little chance of ambulation.

CINEPYELOGRAPHY.

Hanley, H. G. *Proc. Roy. Soc. Med.* **49:** 342, 1956; through Ciba Literature Review **1:** 303 (Oct.) 1956.

A technic is described in which intravenous urography is used to film the excretion of a contrast medium. Film sequences showing the movement of the calyx, ureteric "peristalsis," and the emptying mechanisms indicate that many previously accepted views will have to be revised. This technic also has clinical significance. Cinepyelography may perhaps make it possible to decide which cases of hydronephrosis are suitable for plastic repair. A hydroureter is seldom completely inactive, and the term "atonia"—even with respect to the dilated ureters of pregnancy—is a misnomer. The degree of rigidity of the bladder wall, as seen during this procedure, may possibly indicate the extent of muscular infiltration in bladder carcinoma. Demonstration of the rigidity of a calyx in "preclinical" tuberculous lesions and investigation of reflux in tuberculous cystitis should prove of great clinical value.

OBSERVATIONS ON THE AETIOLOGY OF CHOLELITHIASIS.

Horn, G. *Brit. M. J.* **2:** 732 (Sept. 29) 1956.

An investigation was made of the incidence of cholelithiasis among hospital patients and necropsy material. The related incidence in each age and sex group was defined as the ratio of the number of cases in each group to the population of Great Britain in the corresponding group (Census 1951, 1 per cent sample). Data from 783 patients were examined. The related incidence of cholelithiasis was highest in women in the 50–59 year age group and in males of the 70–79 year age group. At all ages, the frequency was higher in women than in men, but the differences became smaller at ages 80 to 89 years. Below the age of 50 years, gallstones were more frequent in married women without children than in single women, and more frequent in married women with children than married women without children. After the age of 49 years, the related incidence was higher in married nulliparae than in married women with children. Below the age of 50, women with gallstones were heavier than normal women of comparable age and height. After age 50, no differences in weight were apparent. The necropsy records for 492 patients with gallstones were examined. These patients were classified according to age and sex and related to the distribution by age and sex of all necropsy patients (5,699) examined during the same eight-year period. It is thought that if the information derived from postmortem material were combined with that from clinical material, a more accurate description of the distribution of gallstones among a living population might be obtained than from consideration of either set of data alone. In both sexes, the incidence of gallstones was found to increase with age and to be the highest in the oldest age group. In both sexes, gallstones of the asymptomatic variety were more frequent in each age group than were symptomatic stones. It was concluded that, in women, age changes in the incidence of cholelithiasis are modified by factors operating in, and related to the child-

bearing period. After the menopause, sex differences in the incidence of cholelithiasis tend to diminish, so that there is practically no difference in incidence in the oldest age groups. The incidence of gallstones is compared with that of atherosclerosis. It is suggested that in the younger age group there is a sex difference in the metabolism of cholesterol. This difference may be expressed in women by a high frequency of cholelithiasis and a low frequency of atherosclerosis, whereas the reverse occurs in men. After the menopause, when differences in hormonal output between the two sexes are less, the pathways of cholesterol metabolism may converge and thus account for the lessened sex differences in the related incidence of gallstones and atherosclerosis among the older age groups.

ZUR MEDIKAMENTÖSEN BEHANDLUNG VON HERZNEUROSEN (THE MEDICAL MANAGEMENT OF CARDIAC NEUROSIS).

Kron, R. *Praxis* **45:** 872, 1956; through Ciba Literature Review **1:** 295 (Oct.) 1956.

Patients suffering from so-called cardiac neurosis complain of mild periodic attacks of palpitation accompanied by restlessness, a feeling of oppression, disturbed cardiac rhythm, stabbing pains in the region of the heart, and insomnia. Such patients normally have occupations that tax their powers to the utmost. The tensions and disappointments from which they suffer at work are projected onto the circulatory system, especially the heart. Medical therapy must be aimed at interrupting the vicious cycle by damping the patient's neurovegetative reactivity. Fifty patients with cardiac neurosis were treated with Serpatonil, receiving one or two tablets morning and midday. In this way, the effect of Ritalin is exploited during the day, while in the evening and at night the more prolonged action of Serpasil takes over. Whereas Ritalin has a mild stimulating effect, Serpasil relaxes the patient, helping him to conserve his energy and thereby enhance his performance. Shortly after the initiation of Serpatonil treatment, the physical symptoms became less severe and the tendency to moodiness and depression receded. This helped to make the patient more amenable to psychotherapy. Although Serpatonil was administered for several months at a time, no signs of habituation or addiction were observed. In hypotensive and normotensive patients, the blood pressure remained unchanged. In hypertensive patients it is advisable to give an additional dose of 0.25 to 0.5 mg. of Serpasil in the evening.

PODCIŚNIENIE W NEUROCHIRURGII W ŚWIETLE PIERWSZYCH DOŚWIADCZEŃ KLINIKI NEUROCHIRURGICZNEJ A.M. W KRAKOWIE (HYPOTENSION IN NEUROSURGERY REVIEWED IN THE LIGHT OF STUDIES UNDERTAKEN AT THE NEUROSURGICAL CLINIC OF CRACOW MEDICAL ACADEMY).

Lechowski, S., and Szwagrzyk, E. *Neurol. neurochir. psychiatr. polska* **6:** 13, 1956; through Ciba Literature Review **1:** 292 (Oct.) 1956.

Using Pendiomid (N,N,N′,N′-3-pentamethyl-N,N′-diethyl-3-azapentylen-1,5-diammonium dibromide) for the technic of controlled hypotension, 39 intracranial operations and 1 spinal cord operation were performed. The initial dose was 20 to 30 mg. The total dosage averaged 65 mg. Patients varied considerably in their responses to the drug. In 2 patients, even a dosage as high as 200 to 300 mg. proved inadequate. After the first injection of Pendiomid, the blood pressure declined on the average by 35 mm. Hg. A second dose of Pendiomid reduced the pressure by a further 25 mm. Hg. The operation was usually performed at a blood pressure level of roughly 70 mm. Hg, although in some cases the pressure was about 90 mm. A reduction in pressure of this degree is sufficient to insure satisfactory operating conditions. Operational bleeding was markedly reduced in 26 patients, and significantly reduced in 12. This meant that blood transfusions were required on a much smaller scale than would normally have been the case. Use of the hypotensive technic also shortened the duration of the operation and made it easier to remove highly vascularized tumors. No postoperative complications occurred.

ERWEITERUNG DER MAGENDIAGNOSTIK DURCH DEN NACHWEIS PATHOLOGISCHER EIWEISSKÖRPER IM MAGENSAFT (WIDENING OF GASTRIC DISEASE DIAGNOSIS BY THE DETECTION OF PATHOLOGIC PROTEIN BODIES IN THE GASTRIC JUICE).

Norpoth, L.; Surmann, Th.; Wieneken, A., and Clösges, J. *Aerztl. Wchnschr.* **11:** 150, 1956; through Ciba Literature Review **1:** 298 (Oct.) 1956.

Two protein fractions are contained in the gastric juice secreted by the normal stomach, *i.e.*, mucoprotein and gastric juice albumin. Among 19 patients free of stomach ailments, the protein values of the gastric juice varied between 110 and 700 milligrams per cent. The differences in the acid content were considerable. Besides normal acid levels, hypoacid and hyperacid levels were also recorded. Six patients with duodenal ulcer had protein values ranging from 140 to 270 milligrams per cent. The acid levels in these patients were either excessive or bordering on the upper limits of normal. Increases in the protein values (320 to 1,008 milligrams per cent) were demonstrated in 5 patients with gastritis. In 2 of them, no mucoprotein was present, and the anacidity proved refractory to histamine. One patient with gastric ulcer accompanied by hypertrophic gastritis had protein values between 296 and 596 milligrams per cent in the individual fractions of the gastric juice. The pattern of the gastric juice acidity curve was normal. In 2 patients with pernicious anemia, the protein content of the gastric juice varied from 466 to 1,084 milligrams per cent. There was no mucoprotein. The following conclusions can be drawn from these findings: in diseases accompanied by organic changes in the gastric mucosa, pathologic protein bodies appear in the gastric juice. Since the proteins in the gastric juice of patients with duodenal ulcer in this series were found to be normal, it is probably incorrect to assume that duodenal ulcer is always accompanied by gastritis.

RESERPINE FOR THE TREATMENT OF PSYCHOPATHIAE.

Okamoto, S.; Fujita, S.; Kimura, S.; Inoue, K.; Ofuji, T., and Uriu, M. *No to Shinkei* (*Brain and Nerve*) **2:** 502, 1956; through Ciba Literature Review **1:** 296 (Oct.) 1956.

This paper deals with the therapeutic responses elicited with Serpasil in 125 cases of mental disease. Forty-seven in-patients received 4 to 8 mg. of Serpasil daily, and 78 out-patients received 2 to 8 mg. daily. Initially, the drug was generally given intramuscularly. Later, the doses were reduced and oral treatment given instead. The courses of treatment lasted for periods up to three months. Among 48 patients with schizophrenia, 6 were in a state of remission and 26 improved. The fact that Serpasil was sometimes discontinued too soon partly accounted for the failures recorded. Of 5 manic patients, 2 were cured and 1 improved. The types of depression (30 patients) which responded best were the reactive, senile, and agitated forms. Particularly impressive results were achieved in the 17 patients with arteriosclerosis, as 15 of them showed improvement. Among 3 patients with senile dementia, only 1 responded well. Of the 18 patients with neuroses or reactive psychoses, 9 responded with more or less marked improvement. Treatment was also successful in 3 of 4 cases involving hallucinations and excitation states due to paralysis or chronic alcoholism. In general, Serpasil was well tolerated. It is thus suitable for use on an out-patient basis as well as for prolonged courses of treatment.

INTRACAVITARY ADMINISTRATION OF RADIOACTIVE COLLOIDAL GOLD (Au^{198}) FOR THE TREATMENT OF MALIGNANT EFFUSIONS. A REPORT OF THIRTY ONE CASES AND AN APPRAISAL OF RESULTS.

Osborne, M. P., and Copeland, B. E. *New England J. Med.* **255:** 1122 (Dec. 13) 1956.

Seventeen patients with peritoneal effusion due to disseminated carcinoma were treated with doses between 87 and 107 millicuries of radioactive colloidal gold administered through

a trochar or with catheters introduced at laparotomy. In 2 patients good control of the tendency to reform ascites was demonstrated, in 3 there was some tendency towards lessened ascites formation but no useful palliation, and in 7 no benefit was experienced. Five patients died too soon for results to be appraised. In these cases, the duration of survival was not considered the equivalent of useful palliation, and this may account for a discrepancy between these results and those reported by others. Fourteen patients with malignant pleural effusions were treated. The dose of radioactive colloidal gold ranged from 69 to 106 millicuries and was placed in the chest by a thoracentesis needle. Eight patients had good results with control of fluid so that further thoracenteses were not required for two to twenty-seven months. In these 8 patients results of cytologic examination of thoracentesis fluid were positive, and in all the palliative effect of therapy was striking. The carcinomas in this group originated in the breast in 5, in the ovary in 2, and in the lung in 1. Two patients were not benefited, one requiring additional thoracenteses and the other becoming disabled by reaccumulation of fluid. The results could not be evaluated in 4 patients who died within three weeks. No radiation sickness, bone marrow depression, or incidental radiation injury to personnel concerned with the care of the patients occurred. It is essential to establish a certain tissue diagnosis to substantiate disseminated carcinoma as the cause of an effusion. Disappearance of tumor cells was observed following therapy with radioactive gold. No single tumor seemed to bear a more favorable prognosis than another. The results were better in the treatment of pleural metastases. The ideal patient for therapy of malignant effusion with radioactive colloidal gold appears to be one whose chief problem is accumulation of fluid in the chest or abdomen but who is not severely debilitated nor approaching a terminal state. Radioactive colloidal gold offers a safe, predictable, and useful therapy. A prediction is given of its usefulness for prophylactic radiation in favorable cases of ovarian carcinoma.

OSSERVAZIONI CLINICHE SU DI UN NUOVO IPOTENSIVO E SEDATIVO IN GERIATRIA (CLINICAL OBSERVATIONS ON A NEW HYPOTENSIVE AND SEDATIVE AGENT IN GERIATRICS).

Rizzente, S. *Arch. psicol. neurol.* **17:** Suppl. 342, 1956; through Ciba Literature Review **1:** 293 (Oct.) 1956.

This study indicates that Serpasil is useful in the treatment of fixed hypertension in senile patients. The author treated 45 hypertensive subjects between the ages of 63 and 92 years who suffered from arteriosclerotic vascular disease with myocardial damage or valvular lesions but without circulatory failure. Some of them were suffering from the after-effects of hemiplegia or from softening of the brain. The patients complained of marked deterioration in their physical performance and were affected by psychic disorders such as anxiety and excitation. Many were subject to headaches, probably caused by disturbances in the cerebral circulation. Other symptoms included neuralgia, hyperesthesia, and paresthesia. A reduction in systolic and diastolic pressure was elicited in all patients in response to daily doses of 0.5 to 3.0 mg. of Serpasil. Pronounced subjective improvement occurred in 40 of the 45 patients. The tranquilizing properties of Serpasil were particularly evident from the beginning, even when only small doses were given. Because of its beneficial effects and the fact that it is both easy to administer and well tolerated, Serpasil is particularly indicated for senile patients who so often suffer from emotional and nervous upsets.

VASCULAR GRAFTING AND REPLACEMENTS IN THE LATER YEARS.

Roberts, B. *Pennsylvania M. J.* **59:** 1497 (Dec.) 1956.

Three principal types of vascular replacements in use today are 1) homologous arteries, either fresh or preserved, 2) fresh autogenous veins, and 3) prostheses. The majority of homologous artery grafts hold up well and the longest period of use is now nine years. Vein grafts can be expected to last indefinitely. Autogenous vein grafts have the advantage that

they are living tissue that is not replaced. Until prostheses can be demonstrated to be successful in long-term studies, they should be used with caution. Among older persons, arterial obstruction and aneurysm are the most common vascular conditions suitable for grafting. The involvement of an artery by a tumor may call for its replacement. Venous defects are seldom replaceable. Arteriosclerotic occlusions of major arteries, especially those in the leg are common in elderly people. The selection of candidates for grafting depends upon systemic and local factors. Diabetic patients are sometimes suitable for this type of surgery. Patients with extremely ischemic feet usually have extensively diseased arteries and probably will not be suitable candidates for grafts, but even patients with gangrenous toes have been helped by grafts, and pulses have been restored to their feet. In the case of separate areas of obstruction, relieving the most proximal block may be worth while. No attempt should be made to graft arteries distal to the popliteal or brachial arteries. If the popliteal pulse is absent, arteriography should be performed. A satisfactory arteriogram must show not only the occlusion but also the condition of the vessel beyond it. Unless there is a suitable vessel distally, grafting cannot be successful. If there is, a graft of almost any length can be used. Age is not a contraindication to this type of surgery, particularly if it can be limited to the leg. No amputation should be performed for arteriosclerosis without previous arteriography of the limb. Aneurysms are occurring with increasing frequency—most of them in the later years of life. Aortic lesions should be exercised unless the patient cannot survive the major surgical procedure involved. The operative mortality in reasonably good-risk patients should not be above 10 per cent. The mortality of operative treatment of thoracic aneurysms is higher, but here too conservative treatment carries approximately the same risk. The threat also is sufficient to warrant operation in the case of peripheral aneurysms. The excision of aneurysms and their replacement by grafts prolongs life. Operative mortality in patients past the age of 70 years is dropping as more experience is gained. Arterial grafting gives promise of usefulness in the aged.

LEVARTERENOL IN CARDIAC INFARCTION WITH SHOCK AND TRANSIENT COMPLETE HEART BLOCK.

Ruprecht, A. L. *U. S. Armed Forces M. J.* **7:** 1817 (Dec.) 1956.

A case is presented of total heart block that lasted a week after cardiac infarction. During this time, adequate blood pressure was maintained only with the help of Levophed (levarterenol) bitartrate administered as an infusion containing 4 mg. per liter of 5 per cent dextrose in water, at the rate of 20 drops a minute. Blood pressure fell rapidly after onset of the complete block but Levophed restored the patient to pre-shock status in half an hour. Penicillin and later a broad-spectrum antibiotic were given because of sustained fever, the patient placed in an oxygen tent, and heparin sodium and Dicumarol administered. A-V conduction returned after a week of total block. The blood pressure became stabilized at 115/80 mm. Hg. A total of 52 mg. of Levophed bitartrate had been given. After three weeks, no abnormalities of the heart could be detected. One year later, the patient had no more severe cardiac symptoms than prior to the attack. Although the value of levarterenol in shock from a cardiac infarct is established, attention is drawn to patients in whom shock and A-V dissociation occur together, and to the unique features that they present. Cardiac infarcts causing A-V dissociation are often fatal, but the high mortality is in part related to a change in rhythm that may be temporary. Cardiac output falls rapidly after the infarct and may drop lower with the onset of bradycardia, so that hypotension becomes severe. The combination of fresh infarct and slow rate may cause the minute output to decline due to the vicious effect of ischemia on contractile force. The preservation of coronary flow when it can be accomplished by the use of pressor therapy in these cases can result in striking recovery. Pressor therapy minimizes weaknesses arising from prior cardiac lesions. Extension of an infarct is more likely if ischemia is aggravated by a marked fall in blood pressure. Levarterenol may overcome this handicap or abolish the arrhythmia and simplify recovery. Fever in combination with a fixed ventricular rate represents a grave

threat to persons with a low stroke capacity. Sustaining pressure by a contraction of the vascular bed, levarterenol is helpful in such patients, as illustrated by the case presented. The use of levarterenol to sustain coronary flow during the crucial phase in patients with infarcts of the heart and complete A-V block may permit more of them to survive and regain their cardiac function. The availability of safe agents for raising the ventricular rate offers an added opportunity for treatment of such patients.

RESERPINE (SERPASIL) IN MINOR PSYCHIATRY. PRELIMINARY REPORT.

Seth, A. K., and Nath, V. *Indian J. M. Sc.* **10:** 391, 1956; through Ciba Literature Review **1:** 297 (Oct.) 1956.

Serpasil was used to treat ambulatory patients with psychic disorders unaccompanied by physical disease. The principal symptoms observed among these patients were anxiety, hyperexcitability, perseveration, insomnia, confusional states, poor concentration, disturbances of memory, and irritability. Treatment was initiated with average daily doses of 0.75 mg. of Serpasil orally and the dosage later gradually reduced. For maintenance, one evening dose of 0.125 mg. of Serpasil often proved sufficient. The results obtained were, in general, good. The patients usually began to improve on the third treatment day. The first symptoms to disappear were anxiety and hyperexcitability. The blood pressure of these patients, all of whom were normotensive, underwent no change.

A MORE AGGRESSIVE APPROACH TOWARD THE RESTORATION OF BLOOD FLOW IN ACUTE ARTERIAL INSUFFICIENCY.

Shaw, R. S. *Surg., Gynec. & Obst.* **103:** 279 (Sept.) 1956.

The reconstructive surgical methods and rationale applied to problems of chronic arterial insufficiency should also be used in the treatment of acute arterial insufficiency. Survival of the extremity is too frequently taken as the criterion of successful treatment of acute arterial occlusion. The survival of a limb with persisting symptoms of arterial insufficiency is not a good result, if an asymptomatic extremity can be obtained by surgical restoration of arterial continuity. This report describes the application of these principles to cases of acute arterial occlusion by emboli and arteriosclerotic thrombus which by older standards would not have been considered amenable to surgery. Fourteen cases are reported of acute arterial insufficiency due to thrombosis of arteriosclerotic vessels and arterial embolization with extensive secondary thrombosis. These patients were treated by the correction of the primary obstructing process and with special attention to the removal of secondary thrombi. The results justify the recommendation that the restoration of normal arterial flow in cases of embolism and possibly in all acute arterial occlusion be the primary objective in treatment. The best results will be obtained by prompt restoration of the circulation before serious ischemic damage and the propagation of distal thrombus has had a chance to occur. Good flow is of greater importance in preventing postoperative thrombosis than is anticoagulant therapy. Postoperative anticoagulant therapy is unnecessary when good flow has been established following arterial grafting, and may not be of help in preventing thrombosis when the flow is poor.

SYMPOSIUM ON HORMONES AND CANCER THERAPY.

Am. J. Med. **21:** 659–738 (Nov.) 1956.

This symposium presents an appraisal of the current status of hormones and cancer. The comments of guest editor Alfred Gellhorn, M.D., in the Foreword, are as follows: *1. Kirschbaum, A. Endocrine Aspects of Experimental Neoplasia.* This paper introduces the discussion of hormones and cancer with particular emphasis on their importance in tumorigenesis as shown in laboratory animals. Attention should be given to the concept of tumor dependence and autonomy which has emerged from this experimental work, since the success of hormone modification in the treatment of human cancers appears to rest on this issue. Dr.

Kirschbaum brings out the interesting fact that endocrine ablations or the administration of sex hormones do not affect the natural history of spontaneous cancer of the breast in mice; these measures, however, if initiated early in the life of mice can prevent the development of tumors in strains that have a high spontaneous incidence of the disease. *2. Hertz, R. Physiologic Effects of Androgens and Estrogens in Man.* Dr. Hertz assesses the importance of hormone stimulation in the genesis of cancers in hormone-dependent organs in man and finds that there is little evidence to indicate that this is a major factor. His lucid summary of the physiologic effects of the gonadal steroids provides a firm foundation for recognizing the "side effects" of hormone therapy in patients with cancer. Particularly valuable is the discussion of the metabolic actions of the hormones, since these are of importance in explaining therapeutic benefits that may occur even when there is no apparent tumor inhibition. *3. Dorfman, R. I. Metabolism of Androgens, Estrogens and Corticoids.* This paper provides an essential background for the proposed rationale of adrenal and pituitary ablation. The metabolism of the sex hormones and adrenal cortical steroids, the question of androgen conversion to estrogen, and the extent of androgen and estrogen secretion by the adrenal cortex are among the topics discussed. *4. Taylor, S. G., III. Hormonal Modification in the Treatment of Disseminated Cancer of the Breast.* The paper by Dr. Taylor provides a guide to the pragmatic use of androgens and estrogens in the treatment of cancer of the breast together with brief mention of his experience with adrenalectomy and hypophysectomy. The value and advantages of estrogens for the postmenopausal patient have been emphasized. The recommendations for the sequence of hormone modification in the various types of clinical problems which are seen in cancer of the breast are instructive. *5. Whitmore, W. F., Jr. Hormone Therapy in Prostatic Cancer.* This is a comprehensive discussion of clinical aspects of prostatic cancer with emphasis on diagnosis and therapy in relationship to the natural history of the tumor. The status of androgen deprivation therapy with an evaluation of the effect of this regimen on survival time establishes its usefulness for palliation. The limited value of adrenalectomy and probably of hypophysectomy in the management of recurrent prostatic carcinoma emphasizes again the importance of tumor autonomy as the major cause of failure of hormone therapy in cancer. *6. Baker, W. H. Abnormalities in Calcium Metabolism in Malignancy; Effects of Hormone Therapy.* The frequency of skeletal metastases from carcinomas of the prostate and breast is high and the associated disturbances in mineral metabolism constitute one of the major complications of disseminated cancer of the breast. Dr. Baker presents the problem of hypercalcemia instructively and relates the influence of hormones both to the genesis of the metabolic disturbance and to its treatment. The discussion of the usefulness and limitations of urinary calcium excretion studies for the evaluation of therapeutic measures in cancer of the breast introduces valuable words of caution for clinical investigators. *7. Kennedy, B. J. Extirpative Endocrine Therapy for Advanced Cancer of the Breast.* Dr. Kennedy presents an appraisal of the contribution of castration, adrenalectomy, and hypophysectomy in the treatment of disseminated cancer of the breast. Attention is drawn to the value of ovariectomy in the premenopausal patient with metastatic cancer of the breast and the necessity for adequate ovarian radiation dosage if this technic is elected for castration. The problems of long-term maintenance in the adrenalectomized patient are discussed and it is suggested that the analogous situation in the hypophysectomized individual is less difficult. It is emphasized that the place of hypophysectomy in the treatment of cancer of the breast is still being defined and it is not surprising, therefore, that Dr. Kennedy and Dr. Taylor are not in agreement on the relative merits of this procedure as compared to bilateral adrenalectomy. In any event, both point out the importance of tumor dependence on hormone as a requisite for therapeutic benefit from any of the extirpative procedures, and from this it follows that such information constitutes the major criterion for the selection of patients for adrenalectomy or hypophysectomy. *8. Luft, R.; Olivecrona, H.; Ikkos, D.; Nilsson, L.-B., and Ljunggren, H. Hypophysectomy in the Treatment of Malignant Tumors.* These authors, who pioneered in the use of hypophysectomy for the treatment of cancer of the breast, present a conservative and critical summary of their own experience.

Histologic study of the sella turcica at necropsy revealed that pituitary removal was incomplete in a significant number of cases. In spite of this, objective regression of the tumor could occur. Whether or not the presence of pituitary tissue was an important factor in any of the therapeutic failures or in the duration of remissions achieved cannot be evaluated. The finding does emphasize, however, that complete hypophysectomy is technically difficult. The results in a small number of patients with prostatic cancer are provocative and even though the collected experience cited by Dr. Whitmore is not encouraging, further evaluation would appear to be indicated.

NEWS AND NOTICES

THE BURKE FOUNDATION REHABILITATION CENTER

White Plains, New York

An extensive renovation of the third floor of the main administration building of The Burke Foundation Rehabilitation Center, Mamaroneck Avenue, White Plains, N. Y., has recently been completed, according to Edward J. Lorenze, M.D., Medical Director.

The new 15-bed Rehabilitation Unit is modern in every respect. It has 11 private rooms and two luxurious double rooms with private baths. Hand basins have been installed in each private room and there has been general renovation and alteration throughout. The rooms and corridors are painted in attractive pastel colors with harmonizing bed spreads, window draperies and chair coverings. All new hospital furniture of the latest modern design has been installed.

This addition brings the bed capacity to 150 beds, of which 50 are for the rehabilitation of patients with neuro-musculo-skeletal disabilities.

The unit has its own pantry for preparing special diets and serving meals provided by the central kitchen. It has an attractive central lounge for television viewing and other recreational activities. It also has an ultra-modern glassed-in nurses' station and private doctors' examining room.

The renovation, which cost approximately $50,000, was contributed to by a grant from the Ford Foundation.

THE NINTH POSTGRADUATE ASSEMBLY IN ENDOCRINOLOGY AND METABOLISM

Sponsored by The Endocrine Society, The Medical College of Georgia, and The Medical College of Georgia Foundation, Inc.

Augusta, Georgia

October 21–25, 1957

The faculty will consist of 22 eminent clinicians and investigators from various parts of the country in the fields of endocrinology and metabolism. The program will cover the various endocrinopathies, with emphasis on the clinical aspects, demonstration of laboratory tests, presentations of cases, and question and answer panel discussions. The course is designed to cover the main aspects of diagnosis and therapy in the field of endocrinology and metabolism for the physician in general practice and for those in other specialties who wish to have a general knowledge of this rapidly growing field.

A syllabus with brief abstracts of lectures will be available to the registrants at the time of the Assembly.

The course has been approved by the American Academy of General Practice for 35 credit hours in Category 1.

For further information concerning the program and registration, write to *Dr. Robert B. Greenblatt, Department of Endocrinology, Medical College of Georgia, Augusta, Georgia.* Registration is limited to 100; tuition fee is $100.00. Rooms will be reserved for the students and faculty at the Bon Air Hotel. Residents and fellows will be admitted for $35.00.